UNITED STATES DISTRICT COURT
FOR THE NORTHERN DISTRICT OF OHIO
EASTERN DIVISION

IN RE NATIONAL PRESCRIPTION OPIATE LITIGATION	MDL No. 2804 Case No. 17-md-2804
This document relates to:	Hon. Dan Aaron Polster
The County of Summit, Ohio, et al. v. Purdue Pharma L.P., et al. Case No. 18-op-45090	
The County of Cuyahoga, Ohio, et al. v. Purdue Pharma L.P., et al Case No. 17-op-45004	

EXPERT REPORT OF PROFESSOR EDWARD MICHNA, J.D., M.D.
MAY 10, 2019

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I. INTRODUCTION AND QUALIFICATIONS

A. Assignment

1. I have been retained by Cephalon, Inc. ("Cephalon"), Teva Pharmaceuticals USA, Inc. ("Teva"), Actavis Pharma, Inc. ("Actavis Pharma"), Actavis LLC ("Actavis LLC"), Watson Laboratories, Inc. ("Watson"), and other affiliates[1] to serve as an expert witness in this case.

2. It is my understanding that the Plaintiffs allege that the Teva Defendants engaged in off-label and other marketing that misrepresented the risks and overstated the benefits of Actiq and Fentora. Plaintiffs allege that this false marketing deceived physicians into writing medically unnecessary prescriptions for Actiq and Fentora that resulted in reimbursements that they would not have otherwise paid and other alleged damages associated with the opioid abuse crisis.

3. I have been asked: (a) to comment on the FDA rules applicable to the prescribing of Actiq and Fentora; (b) to comment on the efficacy of opioids to treat chronic pain; (c) to comment on the concept of breakthrough pain and the efficacy of Actiq and Fentora to treat breakthrough pain; (d) to examine and explain the FDA-required Risk Evaluation and Mitigation Strategies (REMS) in place for transmucosal immediate release fentanyl (TIRF) products, including what prescribers and patients must acknowledge

[1] Teva USA and Cephalon are referred to as the "Teva Defendants." Actavis Pharma, Actavis LLC, Watson, Warner Chilcott Company, LLC, Actavis South Atlantic LLC, Actavis Elizabeth LLC, Actavis Mid Atlantic LLC, Actavis Totowa LLC, Actavis Kadian LLC, Actavis Laboratories UT, Inc. f/k/a Watson Laboratories, Inc.-Salt Lake City, and Actavis Laboratories FL, Inc., f/k/a Watson Laboratories, Inc.-Florida are referred to as the "Actavis Generic Defendants." In addition, I understand that Teva Pharmaceutical Industries, Ltd. ("Teva Ltd.") has been named as a Defendant based upon the conduct of the Teva and Actavis Generic Defendants, but contests personal jurisdiction. Accordingly, the opinions stated herein as to the Teva and Actavis Generic Defendants also apply to Teva Ltd.

understanding before prescriptions of those medicines can be written; and (e) to evaluate the assumption that all marketing, including detailing, is false, including marketing materials attributable to the Teva Defendants.

B. Qualifications

4. I am an Assistant Professor of Anesthesia at Harvard Medical School. I am also Staff Anesthesiologist at the Pain Management Center, Brigham and Women's Hospital and Clinical Staff, Anesthesia, at Dana-Faber Cancer Institute. I am currently the Director of Pain Trials Center, Department of Anesthesia, Brigham and Women's Hospital. From 2001-2010, I was the Director of Interventional Pain Management, Dana-Faber Cancer Institute.

5. Since 2009, I have been a part-time consultant of the Food and Drug Administration, Drug Advisory Committee on anesthesia and analgesia.

6. At Harvard Medical School, I teach pain management and anesthesia to fellows, residents, and medical students.

7. I obtained my M.D. from the UMDNJ–New Jersey Medical School in 1991. I also obtained a J.D. from Seton Hall Law School, New Jersey in 1985. I did a residency in anesthesia and a fellowship in pain, both at Brigham and Women's Hospital. Prior to becoming an assistant professor, I was a clinical fellow and a clinical instructor at Harvard Medical School.

8. I have published over 50 peer-reviewed academic articles over the course of my career to date. My articles have been published in the top journals in pain medicine: Radiology, Pain, Clinical Journal of Pain, Anesthesiology, and Pain Medicine, among others.

9. Over the years, my research has included overseeing FDA registration trials (phases 2 and 3) for pain medications and medications for symptom relief. Another major part of my clinical research has involved the development of opioid prescribing risk mitigation strategies, and assessing the clinical effects of those strategies.

10. I currently bill for my services at $800 per hour. My compensation for the work on this matter is not contingent upon the outcome of this litigation or on the content of the opinions that I offer in this case. Appendix A provides my Curriculum Vitae, which includes a list of my expert testimony within the past four years.

C. Facts and Data Considered

11. The opinions and analysis presented in this report are based on currently available information, and I reserve the right to supplement or amend this report if I receive additional information that warrants such a supplement or amendment. A list of the materials I have considered in forming my opinion is attached as Appendix B.

II. OVERVIEW OF TEVA DEFENDANTS' TIRF PRODUCTS AND RELATED PLAINTIFFS' ALLEGATIONS

12. Actiq is an oral transmucosal buccal fentanyl lozenge that was approved by the FDA in November 1998 for the "management of breakthrough pain in cancer patients 16 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain."[2] Actiq was initially developed by Anesta Corporation and marketed by Abbott Laboratories.[3] Cephalon purchased Anesta

[2] "Actiq Label, November 1998," 1998, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/20747lbl.pdf.

[3] "Actiq Label, November 1998," p. 30.

in 2000, and has since been responsible for the promotion, distribution, and sale of Actiq.[4]

13. Fentora is an oral transmucosal buccal fentanyl tablet that was approved by the FDA on September 25, 2006 for the "management of breakthrough pain in cancer patients 18 years of age and older who are already receiving and who are tolerant to around-the-clock opioid therapy for their underlying persistent cancer pain."[5]

14. Actiq and Fentora are members of the TIRF class of medications.[6] Other TIRF medicines include Abstral fentanyl sublingual tablets, Lazanda fentanyl nasal spray, Onsolis fentanyl buccal soluble film, Subsys fentanyl sublingual spray, and approved generic equivalents.[7] These medications, along with other opioids, are all subject to strict controls under the Controlled Substances Act (CSA) as they are designated Schedule II medicines, meaning that they are known to have a currently accepted medical use in treatment in the United States but they carry a high potential for abuse, which may lead to severe psychological or physical dependence.[8]

15. Since the time of launch, both Actiq and Fentora have had FDA-approved risk management programs ("RMPs") in place, designed to educate the various stakeholders with the goal of protecting patients from serious safety hazards. For Actiq, this was called

[4] In 2000, Cephalon also acquired U.S. marketing rights to Actiq from Abbott Laboratories. *See* Cephalon, Inc., Form 10-K405, filed March 30, 2001, p. 31. Cephalon did not begin promoting Actiq until 2001.

[5] "Fentora Label, September 2006," 2006, available at https://www.accessdata.fda.gov/drugsatfda_docs/label/2017/021947s019lbl.pdf, pp. 1, 11.

[6] See, e.g., FDA, *Addendum to the FDA briefing information to summarize TIRF REMS issues relevant to the August 3, 2018 meeting*, July 25, 2018.

[7] TIRF REMS Access, "Education Program for Prescribers and Pharmacists," available at https://www.tirfremsaccess.com/TirfUI/rems/pdf/education-and-ka.pdf.

[8] U.S. Drug Enforcement Agency, "Drug Scheduling," available at https://www.dea.gov/drug-scheduling, accessed April 24, 2019.

the Actiq RMP; for Fentora it was called the Fentora Risk Minimization Action Plan ("RiskMAP"). In 2010, the FDA determined that a REMS would be necessary for the entire class of TIRF products to mitigate the potential for harm, particularly in opioid non-tolerant patients who were at risk for life-threatening respiratory depression.[9] The initial TIRF REMS was approved on December 28, 2011 and launched on March 12, 2012. In the ensuing years, there have been several updates to account for the introduction of new products/formulations, label changes, and enhanced knowledge about the products and the TIRF REMS system.[10]

16. Plaintiffs contend "that all prescriptions of opioids for chronic pain in the Bellwether Jurisdictions [Summit County, Cuyahoga County] were written in reliance on [...] misrepresentations, omissions, and wrongdoing."[11] Further, Plaintiffs assert that "Defendants' deceptive marketing also increased the comfort level of doctors and patients in prescribing opioids for acute trauma and post-operative pain. [...] As a result of Defendants' misleading marketing regarding the safety of prescription opioids, doctors were comfortable writing prescriptions for longer durations than necessary to cover the likely period of acute pain."[12]

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[9] See, e.g., FDA, *Addendum to the FDA briefing information to summarize TIRF REMS issues relevant to the August 3, 2018 meeting*, July 25, 2018.

[10] FDA, "Approved Risk Evaluation and Mitigation Strategies," September 7, 2017, available at https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=60, accessed February 14, 2019.

[11] Summit County, Cuyahoga County, and the Cities of Akron and Cleveland, Ohio Plaintiffs' Responses and Objections to Manufacturer Defendants' Fourth Set of Interrogatories, *In Re: National Prescription Opiate Litigation* Case No. 17-md-2804, United States District Court for the Northern District of Ohio Eastern Division, ("Plaintiffs' Responses and Objections to Manufacturer Defendants' Fourth Set of Interrogatories"), p. 7.

[12] Plaintiffs' Responses and Objections to Manufacturer Defendants' Fourth Set of Interrogatories, p. 8; *see also* Third Amended Corrected Complaint, *In Re: National Prescription Opiate Litigation*, May 29, 2018 ("Complaint"), ¶ 169.

17. Plaintiffs allege that this alleged deceptive marketing took many forms, including detailing visits by sales representatives; continuing medical education programs ("CMEs"); the distribution of third-party publications; and speaker events, such as other peer-to-peer programs.[13] Plaintiffs contend that the Teva Defendants' marketing "deprived prescribers and patients of the ability to make informed choices about whether, when, and which opioids to prescribe and use, for how long, and at what doses."[14]

18. Specifically, Plaintiffs and Plaintiffs' experts assert that the Teva Defendants violated their responsibilities under the Food Drug and Cosmetics Act by promoting the use of Actiq and Fentora for off-label indications—that is, for conditions that were not indicated by Actiq's or Fentora's FDA-approved labels.[15]

III. SUMMARY OF OPINIONS

19. I have reached the following conclusions to a reasonable degree of certainty.

20. First, the FDA recognizes that physicians may prescribe an approved medicine for any use, including uses that are not listed in the FDA-approved labeling. The practice is commonly referred to as "off-label" prescribing.

[13] Plaintiffs' Responses and Objections to Manufacturer Defendants' Fourth Set of Interrogatories, p. 12 ("Bellwether Plaintiffs contend that [Defendants misrepresented] the risks, benefits, and superiority of opioids [...] including, but not limited to, through sales visits, continuing medical education and speaker programs, publications and websites, and treatment guidelines"); Complaint, at ¶ 171.

[14] Plaintiffs' Responses and Objections to Manufacturer Defendants' Fourth Set of Interrogatories, p. 12.

[15] See, e.g. Expert Report of David Kessler, M.D., *In Re: National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019 ("Kessler Report"), pp. 201-210 ("Teva marketed Actiq for non-cancer pain, an indication that lacked substantial evidence to support safety[, ...] failed to comply with its risk management obligations in marketing Actiq[,... and] promoted Fentora for non-malignant pain, which lacked substantial evidence to support safety.").

21. Second, the FDA recognizes that off-label prescribing is common and may represent a medically appropriate standard of care. Indeed, off-label use can provide important opportunities for patients to receive care based on the most up-to-date medical and scientific data (which is often not reflected in the FDA-approved labeling) and for physicians to tailor patient treatment plans based on each patient's unique medical needs, circumstances, and preferences.

22. Third, opioids may be effective in treating patients with chronic non-cancer pain, based upon the individual needs, medical history, and circumstances of the patient. In addition, breakthrough non-cancer pain is real, with significant social and physical consequences; it, too, may be treated effectively by opioid medicines, including Actiq and Fentora.

23. Fourth, these principles hold true for Actiq and Fentora. It is the physician's decision whether to prescribe Actiq or Fentora for any given patient based on that patient's unique medical needs, circumstances, and preferences. Actiq and Fentora may be safe and effective for treating non-cancer pain in certain patients.

24. Fifth, from the date of approval, Actiq and Fentora have been subject to FDA-approved risk mitigation programs. Since 2012, prescribers and patients have had to comply with even more rigorous requirements of the TIRF REMS before any Actiq or Fentora prescription can be written and filled.

25. Sixth, the TIRF REMS ensures that prescribers are informed about the risks, benefits, appropriate use, indications, and abuse or overdose potential of TIRF medicines, including Actiq and Fentora.

26. Seventh, the TIRF REMS ensures that patients are informed about the risks, benefits, appropriate use, indications, abuse or overdose potential, of TIRF medicines, including Actiq and Fentora.

27. Eighth, the assumption that all pharmaceutical marketing, including detailing, of opioids involves false and misleading information is misguided. I have reviewed marketing materials that Plaintiffs attribute to the Teva Defendants and it is my opinion that those marketing materials are balanced and reasonable, and are not misleading when read as a whole.

IV. THE FDA DEFERS TO PHYSICIANS IN THEIR DETERMINATION OF WHETHER ACTIQ OR FENTORA REPRESENT THE APPROPRIATE TREATMENT FOR ANY GIVEN PATIENT

A. The FDA Recognizes That Physicians May Prescribe An Approved Medicine For Uses That Are Not Listed In The FDA-Approved Labeling [16]

28. The Federal Food, Drug, and Cosmetic Act (FDCA) grants the FDA the authority to regulate certain aspects of a pharmaceutical manufacturer's conduct through the FDA medicine and labeling approval process. In order for a medicine to be legally marketed, the manufacturer must obtain FDA approval. Once the FDA determines that a medicine's health benefits outweigh its known risks, the medicine is approved for sale.[17] The FDA also must approve the corresponding product label and any product communications by the manufacturer.[18]

[16] FDA, "Standardizing and Evaluating Risk Evaluation and Mitigation Strategies," 2014.

[17] FDA, "Development & Approval Process (Drugs)," available at https://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm, accessed February 14, 2019.

[18] FDA, *An Introduction to the Improved FDA Prescription Drug Labeling*, 2006; FDA, *Medical Product Communications That Are Consistent With the FDA-Required Labeling — Questions and Answers; Guidance*

29. The FDA also has the authority to require pharmaceutical manufacturers to provide written plans to address serious risks associated with medicines. These plans impose additional requirements on the manufacturer of a prescription medicine to ensure prescriber education when the FDA believes certain risks may not adequately be managed with prescription labeling alone.[19] Risk plans are not, however, intended to regulate the practice of medicine, explicitly limit the off-label prescribing of medicines, or tell physicians what is or what is not medically appropriate for a given patient.

30. The FDA "recognizes that once it approves a product for marketing, healthcare practitioners are the most important managers of product risks. … [A]s the Agency has long recognized, the FDCA and FDA regulations establish requirements governing the safety and effectiveness of medical products. The FDA does not have authority under these provisions to control decisions made by qualified healthcare practitioners to prescribe products for conditions other than those described in FDA-approved professional labeling, or to otherwise regulate medical or surgical practice."[20] Indeed, the FDA has expressly acknowledged this point.[21]

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for Industry, June 2018, https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm537130.pdf.

[19] FDA, "FDA's Role in Managing Medication Risks," available at https://www.fda.gov/Drugs/DrugSafety/REMS/ucm592672.htm, accessed February 13, 2019.

[20] FDA, *Guidance for Industry*, *Development and Use of Risk Minimization Action Plans*, March 2005, March 2005, https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071616.pdf (emphasis added).

[21] 37 Fed. Reg. 16,503, 16,503-16,504 (Aug. 15, 1972) ("If an approved new drug is shipped in interstate commerce with the approved package insert, and neither the shipper nor the recipient intends that it be used for an unapproved purpose, the requirements of section 505 of the Act are satisfied. Once the new drug is in a local pharmacy after interstate shipment, the physician may, as part of the practice of medicine, lawfully prescribe a different dosage for his patient, or may otherwise vary the conditions of use from those approved in the package insert, without informing or obtaining the approval of the Food and Drug Administration. [...] Throughout the debate leading to enactment, there were repeated statements that Congress did not intend the Food and Drug Administration to interfere with medical practice and references to the understanding that the bill did not purport to regulate the practice of medicine as between the physician and the patient."); 21 C.F.R. § 312.2(d)

31. The FDA recognizes that physicians may prescribe an approved medicine for any use, including for uses that are not listed in the FDA-approved labeling.[22] Due in part to the fast pace of science in areas of unmet need relative to the lengthy approval process, the FDA-approved label often does not reflect all of the medicine's potential uses as commonly accepted by the medical community. Therefore, appropriate prescribing is determined by the knowledge and judgment of the physician, and not strictly by the labeling standards of the FDA.

32. Consistent with these principles, the FDA's policy has been and remains that "[g]ood medical practice and the best interests of the patient require that physicians use legally available drugs, biologics and devices according to their best knowledge and [*sic*] judgement[,]" regardless of whether the FDA has approved the medicine for that specific use.[23]

33. For these reasons, the FDA did not and could not prohibit off-label prescribing of Actiq or Fentora.

("(d) Unlabeled indication. This part does not apply to the use in the practice of medicine for an unlabeled indication of a new drug product approved under part 314 or of a licensed biological product.").

[22] *E.g.*, 59 Fed. Reg. 59,820, 59,821, 59,825 (Nov. 18, 1994); FDA, "Use of Approved Drugs for Unlabeled Indications," *FDA Drug Bulletin* Vol. 12, No. 1 (April, 1982), pp. 4–5 ("once a [drug] product has been approved for marketing, a physician may prescribe it for uses or in treatment regimens of patient populations that are not included in approved labeling. [...] 'Unapproved' or, more precisely, 'unlabeled' uses may be appropriate and rational in certain circumstances, and may, in fact reflect approaches to drug therapy that have been extensively reported in medical literature. [...] Valid new uses for drugs already on the market are often first discovered through serendipitous observations and therapeutic innovations, subsequently confirmed by well-planned and executed clinical investigations").

[23] FDA, "'Off-Label' and Investigational Use Of Marketed Drugs, Biologics, and Medical Devices - Information Sheet," July 12, 2018, available at http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm, accessed April 23, 2019 and Medical Devices"; 40 Fed. Reg. 15,392, 15,394 (Apr. 7, 1975).

B. Off-label Prescribing Can Represent the Appropriate Standard of Care

34. The FDA has long acknowledged that "accepted medical practice often includes drug use that is not reflected in approved drug labeling."[24] This is because off-label use provides important opportunities for patients to receive care based on the most up-to-date medical and scientific data, which may not be reflected in the FDA-approved labeling. Moreover, off-label usage allows doctors to tailor their patients' treatment plans based on each patient's unique medical needs and preferences.[25] Indeed, off-label uses or treatment regimens may constitute "a medically recognized standard of care."[26]

35. The Centers for Medicare and Medicaid Services (CMS) describes off-label prescribing as "a fundamental component of patient care" that "allows and encourages innovation, [and] enables discovery of benefits not otherwise known."[27] Off-label prescribing is also fundamental to medical care for patient populations not typically included in clinical studies, such as pediatric or geriatric patients.[28]

36. Because off-label uses may constitute the appropriate standard of care, the FDA has expressly recognized the need for physicians and other healthcare professionals to receive

[24] FDA, "Use of Approved Drugs for Unlabeled Indications," *FDA Drug Bulletin* Vol. 12, No. 1 (April, 1982).

[25] E.g., Scott Gottlieb, M.D., *Remarks by Dr. Gottlieb at the FDA Online Opioid Summit*, June 27, 2018, https://www.fda.gov/NewsEvents/Speeches/ucm611945.htm ; 63 Fed. Reg. 31,143, 31,153 (June 8, 1998); FDA, "Use of Approved Drugs for Unlabeled Indications," *FDA Drug Bulletin* Vol. 12, No. 1 (April, 1982).

[26] FDA, "Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices," January 13, 2009, available at http://www.fda.gov/oc/op/goodreprint.html, accessed February 14, 2019; 63 Fed. Reg. 31,143, 31,153 (June 8, 1998); *see also Buckman Co. v. Plaintiffs' Legal Comm.*, 531 U.S. 341, 351 n.5 (2001); *Washington Legal Found. v. Friedman*, 13 F. Supp. 2d 51, 56 (D.D.C. 1998).

[27] CMS, *Pharmacy Self-Auditing*, December 2015, p. 4.

[28] CMS, *Pharmacy Self-Auditing*, December 2015, p. 4 ("Off-label prescribing allows and encourages innovation, enables discovery of benefits not otherwise known, and is a tenet of care for patient populations not routinely included in clinical studies (for example: pediatric and geriatric populations).").

scientific information and data regarding off-label uses.[29] This policy is rooted in the agency's understanding that patient care may be optimized and public health may benefit by increased sharing of high-quality scientific information and data with healthcare providers.

C. Opioids May Be Effective In Treating Non-Cancer Pain.

37. Chronic pain is a serious and debilitating health condition that is estimated to affect at least 50 million people, with significant costs to the economy.[30] The FDA has approved certain opioids for the treatment of chronic non-cancer pain. In my experience, opioids can effectively treat chronic non-cancer pain in appropriate patients.

38. As Schedule II controlled substances, opioid medicines must be prescribed for a legitimate medical purpose—for conditions known to be responsive to the therapy.[31] The decision to prescribe depends on the clinical needs of the patient, and whether the potential benefits outweigh any potential risks for that patient. Patients then need to be monitored for efficacy, side effects, and for any misuse or use for nonmedical purposes.

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[29] *See, e.g.*, 63 Fed. Reg. 64,556, 64,579 (Nov. 20, 1998) (recognizing the "public health gains associated with the earlier dissemination of objective, balanced, and accurate information" about off-label uses); FDA, "Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices" ("FDA does recognize … the important public health and policy justification supporting dissemination of truthful and non-misleading medical journal articles and medical or scientific reference publications on unapproved uses of approved drugs… [T]he public health may be advanced by healthcare professionals' receipt of medical journal articles and medical or scientific reference publications on unapproved new uses of approved or cleared medical products that are truthful and not misleading.").

[30] Dahlhamer J, et al., "Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults — United States," 2016. Morbidity and Mortality Weekly Report (2018), 67:1001–1006, https://www.cdc.gov/mmwr/volumes/67/wr/mm6736a2.htm, accessed May 9, 2019.

[31] U.S. Drug Enforcement Administration, "Practitioner's Manual - Section V - Valid Prescription Requirements," available at https://www.deadiversion.usdoj.gov/pubs/manuals/pract/section5.htm, accessed April 24, 2019 ("To be valid, a prescription for a controlled substance must be issued for a legitimate medical purpose by a practitioner acting in the usual course of professional practice.").

In my own research, I have found that patient characteristics including a family history of substance abuse, past problems with drugs or alcohol, and a history of legal problems correlate strongly with later opioid abuse in chronic non-cancer pain patients.[32] Additionally, my research has shown that controlled substance agreements, regular urine drug screens, and interventions such as motivational counseling are useful tools in minimizing aberrant drug-related behavior among opioid therapy patients.[33] Physicians can use research results of these kinds in screening and monitoring patients for opioid therapy.

39. There may be situations in general where opioids typically would not be utilized, but circumstances warrant a trial exposure. For example, when alternative therapies for pain management have failed to produce the desired effect in a given patient, a doctor may consider prescribing opioids, even if they rarely are used to treat that particular pain-causing condition.

40. Opioids are widely prescribed for non-cancer pain.[34] There are numerous studies and clinical experiences demonstrating a range of safe and effective uses of opioids, including for treating chronic non-cancer pain.[35] One study from 2006 found that "Opioids were

[32] Michna, Edward et al., "Predicting Aberrant Drug Behavior in Patients Treated for Chronic Pain: Importance of Abuse History," *Journal of Pain and Symptom Management* Vol. 28, No. 3 (2004): 250-58.

[33] Jamison, Robert N., Juliana Serraillier, and Edward Michna, "Assessment and Treatment of Abuse Risk in Opioid Prescribing for Chronic Pain," *Pain Research and Treatment* Vol. 2011 (2011): 1-12; Jamison, Robert N. et al., "Substance Misuse Treatment for High Risk Chronic Pain Patients on Opioid Therapy: A Randomized Trial," *Pain* Vol. 150, No. 3 (2010): 390-400.

[34] See, e.g. Levy, Benjamin et al., "Trends in Opioid Analgesic–Prescribing Rates by Specialty, U.S., 2007–2012," *American Journal of Preventive Medicine* Vol. 49, No. 3 (2015): 409-13.

[35] Furlan, Andrea D et al., "Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects," *CMAJ* Vol. 174, No. 11 (2006): 1589-94; Haythornthwaite, Jennifer A. et al., "Outcome of Chronic Opioid Therapy for Non-Cancer Pain," *Journal of Pain and Symptom Management* Vol. 15, No. 3 (1998): 185-94; Collett, B. J., "Chronic opioid therapy for non-cancer pain," *British Journal of Anaesthesia* Vol. 87, No. 1 (2001): 133-43; Simpson, Richard K. et al., "Transdermal fentanyl as treatment for chronic low back pain,"

more effective than placebo for both pain and functional outcomes in patients with nociceptive or neuropathic pain or fibromyalgia."[36] Recently, a study has confirmed the safe use of opioids for pain control in patients with sickle cell disease.[37] Another study of patients from the Johns Hopkins Pain Treatment Center demonstrated that opioid treatment in chronic non-cancer pain patients can be effective at reducing pain intensity without significantly impairing cognition.[38] Furthermore, opioid medications were associated with reduced anxiety, reduced hostility and improved sleep.[39] Patients also have shown a preference for opioid therapy over other treatments due to a favorable impact on pain reduction.[40]

41. This has led some doctors to publicly opine that "it is nonsensical for an opioid analgesic to carry an indication specifically for cancer pain," since chronic pain is common, severe, and disabling in both malignant *and* non-malignant pain patients.[41] Even Plaintiffs concede that these lines are blurry at best, as "in many cases of cancer pain or palliative care, the time period involved is sufficiently long that opioid prescribing considerations are more like those in chronic pain conditions," and "not all 'cancer pain' is associated

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Journal of Pain and Symptom Management Vol. 14, No. 4 (1997): 218-24; Kalso, Eija et al., "Opioids in chronic non-cancer pain: systematic review of efficacy and safety," *Pain* Vol. 112, No. 3 (2004): 372-80.

[36] Furlan et al., "Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects," *CMAJ* Vol. 174, No. 11 (2006): 1589-94.

[37] Akinboro, Oladimeji Akinola et al., "Opioid Use Is NOT Associated with in-Hospital Mortality Among Patients with Sickle CELL Disease in the United States: Findings from the National Inpatient Sample," *Blood* (2018)

[38] Haythornthwaite et al., "Outcome of Chronic Opioid Therapy for Non-Cancer Pain," *Journal of Pain and Symptom Management* Vol. 15, No. 3 (1998): 185-94.

[39] Haythornthwaite et al., "Outcome of Chronic Opioid Therapy for Non-Cancer Pain," *Journal of Pain and Symptom Management* Vol. 15, No. 3 (1998): 185-94.

[40] Collett, "Chronic opioid therapy for non-cancer pain," *British Journal of Anaesthesia* Vol. 87, No. 1 (2001): 133-43.

[41] Passik, S. D. and K. L. Kirsh, "Weighing in on the off-label use of Actiq for noncancer-related pain: a recipe for success or a recipe for disaster?," *Pain Medicine* Vol. 8, No. 2 (2007): 130-3.

with metastatic disease."[42] Physicians use trained judgment about the individual patient in front of them, rather than relying upon absolute distinctions between "cancer pain" and "non-cancer pain."

D. Breakthrough Non-Cancer Pain Is Real And Serious, And Opioids, Including Actiq And Fentora, May Be Effective In Treating Breakthrough Pain

42. While opioids can be effective in controlling chronic non-cancer pain, many patients still experience temporary bursts of pain despite their medication. These temporary exacerbations in otherwise-controlled chronic pain are called "breakthrough pain," and are a well-established reality in pain treatment.[43] Breakthrough pain might be caused by specific circumstances, such as having a more active day than usual. Sharp spikes in pain might also simply be part of a patient's chronic pain condition. While opposing experts equate breakthrough pain with tolerance, these are very different concepts.[44] A patient

[42] Plaintiffs' Responses and Objections to Manufacturer Defendants' Fourth Set of Interrogatories, pp. 10-11.

[43] See, e.g. Portenoy, Russell K et al., "Breakthrough pain in community-dwelling patients with cancer pain and noncancer pain, part 1: prevalence and characteristics," *Journal of Opioid Management* Vol. 6, No. 2 (2010): 97-108; Taylor, Donald R et al., "Impact of breakthrough pain on quality of life in patients with chronic, noncancer pain: Patient perceptions and effect of treatment with oral transmucosal fentanyl citrate (OTFC®, ACTIQ®)," *Pain Medicine* Vol. 8, No. 3 (2007): 281-88; Payne, Richard, "Recognition and diagnosis of breakthrough pain," *Pain Medicine* Vol. 8, Supplement 1 (2007): S3-S7; Smith, Howard, "A comprehensive review of rapid-onset opioids for breakthrough pain," *CNS Drugs* Vol. 26, No. 6 (2012): 509-35, p. 510 ("BTP is highly prevalent in certain patient populations, occurring in 33-55% of patients with chronic cancer pain and ~70% of patients with chronic noncancer pain"); Webster, Lynn R and M. Beth Dove, "Optimizing Opioid Treatment for Breakthrough Pain," 2007, available at www.medscape.org/viewarticle/563417, accessed October 10, 2017.

On cancer-related breakthrough pain specifically, see, e.g. Caraceni, Augusto et al., "Guidelines for the management of breakthrough pain in patients with cancer," *Journal of the National Comprehensive Cancer Network* Vol. 11, Supplement 1 (2013): S-29-S-36; Mercadante, Sebastiano et al., "Factors influencing the use of opioids for breakthrough cancer pain: A secondary analysis of the IOPS-MS study," *European Journal of Pain* Vol. 23, No. 4 (2019): 719-26; Mercadante, Sebastiano et al., "Episodic (breakthrough) pain: consensus conference of an expert working group of the European Association for Palliative Care," *Cancer* Vol. 94, No. 3 (2002): 832-39; Rudowska, Joanna, "Management of breakthrough pain due to cancer," *Contemporary Oncology* Vol. 16, No. 6 (2012): 498-501.

[44] See, e.g. Schuckit, Marc A, "Treatment of opioid-use disorders," *New England Journal of Medicine* Vol. 375, No. 4 (2016): 357-68, pp. 66-67 ("The Pharmaceutical Opioid Industry encouraged and promoted several

developing a tolerance to pain medication might begin to feel their chronic "regular" pain through this medication, but breakthrough pain generally refers to infrequent, sharper spikes felt even if overall pain is generally well managed.

43. In cancer patients, those with breakthrough pain have been found to experience increased levels of anxiety and depression.[45] These patients also have a greater number of pain-related hospitalizations and emergency room visits.[46] In my experience, uncontrolled pain affects mood, generates anxiety, and decreases quality of life. This applies to breakthrough pain due to both cancer and non-cancer pain.

44. Breakthrough pain is a common occurrence with both cancer-related pain and chronic non-cancer pain. Depending upon the exact definitions used for breakthrough pain and the sample of patients selected, studies have estimated that anywhere from 24% to 95% of cancer patients experience breakthrough pain.[47] A 2006 study of 228 chronic pain (including non-cancer pain) patients identified breakthrough pain symptoms in 74% of participants.[48]

misconceptions concerning opioid use, including mischaracterizing addictive behavior as "pseudoaddiction" and tolerance as 'breakthrough pain.'").

[45] Burton, Beth and Giovambattista Zeppetella, "Assessing the impact of breakthrough cancer pain," *British Journal of Nursing* Vol. 20, No. Sup5 (2011): S14-S19.

[46] Fortner, Barry V, Theodore A Okon, and Russell K Portenoy, "A survey of pain-related hospitalizations, emergency department visits, and physician office visits reported by cancer patients with and without history of breakthrough pain," *The Journal of Pain* Vol. 3, No. 1 (2002): 38-44; Abernathy, Amy P., Jane L. Wheeler, and Barry V. Fortner, "A Health Economic Model of Breakthrough Pain," *American Journal of Managed Care* Vol. 14, No. 5 (2008): S129-S40.

[47] Abernathy et al., "A Health Economic Model of Breakthrough Pain," *American Journal of Managed Care* Vol. 14, No. 5 (2008): S129-S40, p. S129.

[48] Portenoy, Russell K et al., "Prevalence and characteristics of breakthrough pain in opioid-treated patients with chronic noncancer pain," *The Journal of Pain* Vol. 7, No. 8 (2006): 583-91.

45. Treating breakthrough pain can involve a combination of increasing the overall level long-acting medication and treating just the breakthrough pain itself. Depending upon patient-specific factors, doctors might be reluctant to increase the day-to-day amount of opioids prescribed. I find that in many cases, I can minimize the amount of opioids needed to address patients' pain by treating the breakthrough pain with immediate-release opioids like Actiq and Fentora, rather than increasing the baseline, day-to-day long-acting opioid level.

46. To treat breakthrough pain, clinical studies have suggested that TIRFs (including sublingual sprays and sublingual fentanyl tablets) can be effective in patients who are opioid tolerant.[49] Rapid-acting opioids, which become active within minutes and last 1-2 hours, have a window of effectiveness that correspond well to the timeline of breakthrough pain. Opioids that are longer-lasting may not be as effective for managing breakthrough pain.[50] Patients with chronic pain have reported a greater pain reduction with fentanyl buccal tablets, versus oxycodone.[51] Patients with chronic cancer and non-

[49] See, e.g. Shimoyama, Naohito et al., "Efficacy and safety of sublingual fentanyl orally disintegrating tablet at doses determined from oral morphine rescue doses in the treatment of breakthrough cancer pain," *Japanese Journal of Clinical Oncology* Vol. 45, No. 2 (2015): 189-96; Nalamachu, Srinivas et al., "Long-term effectiveness and tolerability of sublingual fentanyl orally disintegrating tablet for the treatment of breakthrough cancer pain," *Current Medical Research and Opinion* Vol. 27, No. 3 (2011): 519-30; Minkowitz, Harold et al., "Long-term safety of fentanyl sublingual spray in opioid-tolerant patients with breakthrough cancer pain," *Supportive Care in Cancer* Vol. 24, No. 6 (2016): 2669-75; Mercadante et al., "Factors influencing the use of opioids for breakthrough cancer pain: A secondary analysis of the IOPS-MS study," *European Journal of Pain* Vol. 23, No. 4 (2019): 719-26.

[50] Chang, Andrew et al., "Transmucosal immediate-release fentanyl for breakthrough cancer pain: opportunities and challenges for use in palliative care," *Journal of Pain & Palliative Care Pharmacotherapy* Vol. 29, No. 3 (2015): 247-60.

[51] Ashburn, Michael A et al., "The efficacy and safety of fentanyl buccal tablet compared with immediate-release oxycodone for the management of breakthrough pain in opioid-tolerant patients with chronic pain," *Anesthesia & Analgesia* Vol. 112, No. 3 (2011): 693-702.

cancer pain have also reported better functional improvements with fentanyl buccal tablets, versus short acting opioids.[52]

47. In particular, Actiq and Fentora have been found to successfully treat both non-cancer- and cancer-related breakthrough pain in opioid-tolerant patients.[53] Actiq (and similar medications) can substantially improve several quality of life metrics, including "general activity level."[54] Another study found that treatment with Actiq resulted in significantly better pain reduction than morphine sulfate immediate release in those with breakthrough cancer pain.[55] Fentanyl buccal tablets (including Fentora) have also been found to be "generally safe and well tolerated, with functional improvement in association with chronic noncancer pain."[56]

48. I have also personally seen the efficacy of Fentora in treating breakthrough pain in my own practice. One patient whom I treated had severe neuropathic leg pain. He had failed all neuropathic pain medications, as well as other breakthrough pain opioids. When he

[52] Webster, Lynn R et al., "Fentanyl buccal tablet compared with immediate-release oxycodone for the management of breakthrough pain in opioid-tolerant patients with chronic cancer and noncancer pain: a randomized, double-blind, crossover study followed by a 12-week open-label phase to evaluate patient outcomes," *Pain Medicine* Vol. 14, No. 9 (2013): 1332-45.

[53] Taylor et al., "Impact of breakthrough pain on quality of life in patients with chronic, noncancer pain: Patient perceptions and effect of treatment with oral transmucosal fentanyl citrate (OTFC®, ACTIQ®)," *Pain Medicine* Vol. 8, No. 3 (2007): 281-88; Webster et al., "Fentanyl buccal tablet compared with immediate-release oxycodone for the management of breakthrough pain in opioid-tolerant patients with chronic cancer and noncancer pain: a randomized, double-blind, crossover study followed by a 12-week open-label phase to evaluate patient outcomes," *Pain Medicine* Vol. 14, No. 9 (2013): 1332-45.

[54] Taylor et al., "Impact of breakthrough pain on quality of life in patients with chronic, noncancer pain: Patient perceptions and effect of treatment with oral transmucosal fentanyl citrate (OTFC®, ACTIQ®)," *Pain Medicine* Vol. 8, No. 3 (2007): 281-88.

[55] Coluzzi, Paul H et al., "Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC®) and morphine sulfate immediate release (MSIR®)," *Pain* Vol. 91, No. 1-2 (2001): 123-30.

[56] Fine, Perry G et al., "Long-term safety and tolerability of fentanyl buccal tablet for the treatment of breakthrough pain in opioid-tolerant patients with chronic pain: an 18-month study," *Journal of Pain and Symptom Management* Vol. 40, No. 5 (2010): 747-60.

started Fentora, he was able to continue to work without missing days because of uncontrolled pain. He functioned on this regimen, working as an administrator in the hospital for over five years. He also was able to continue to umpire Little League Baseball during his time, which was one of his passions.

E. Prescribers May Exercise Their Medical Judgment to Prescribe Actiq or Fentora Off-label

49. It is the FDA's policy that "[o]nce a drug or medical device has been approved or cleared by FDA, generally, healthcare professionals may lawfully use or prescribe that product for uses or treatment regimens that are not included in the product's approved labeling … These off-label uses or treatment regimens may be important and may even constitute a medically recognized standard of care."[57] In accordance with this policy, the FDA has stated that "[a]fter FDA evaluates the risks and benefits for the population, the prescriber is central to managing risks and benefits for the individual. In addition, patients make decisions about treatment choices based on their personal valuation of benefits and risks. In the context ***of an individual treatment decision***, FDA's role in reducing risk involves ensuring that accurate, substantiated, and balanced information about a product is available to the prescriber and the patient."[58]

[57] FDA, "Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices," p. 4; *see also* FDA, *Managing the Risks From Medical Product Use Creating a Risk Management Framework*, May 1999, http://www.fda.gov/downloads/safety/safetyofspecificproducts/ucm180520.pdf ("[o]nce medical products are on the market, … ensuring safety is principally the responsibility of healthcare providers and patients, who make risk decisions on an individual, rather than a population, basis."); 68 Fed. Reg. 6,062, 6,071 (Feb. 6, 2003) ("As the FDA has long recognized, its role is neither to regulate physician conduct, nor to train physicians.") and ("The final rule is not intended to establish a standard of care. The rule is designed to provide information and context for health care providers to consider in prescribing certain medications.").

[58] FDA, *Managing the Risks From Medical Product Use Creating a Risk Management Framework*, May 1999, http://www.fda.gov/downloads/safety/safetyofspecificproducts/ucm180520.pdf, p. 22 (emphasis added).

50. The FDA acknowledges that in making this individualized prescribing decision, the FDA approved labeling is not the only factor that a physician considers, because "the labeling of a marketed drug does not always contain all the most current information available to physicians relating to the proper use of the drug in good medical practice" and "advances in medical knowledge and practice inevitably precede labeling revision."[59]

51. The FDA therefore has advised physicians on multiple occasions that when making prescribing decisions for a particular patient, they should rely not only on the information contained in the labeling, but also on other factors, such as any "other adequate scientific data available" to them[60] and their "substantial clinical experience."[61] Indeed, the FDA recognizes that these "[b]enefits and risks are difficult to quantify and compare because they may apply to different individuals and are usually measured and valued differently."[62] FDA further acknowledges that the "assessment and comparison of a product's benefits and risks is a complicated process that is influenced by a wide range of societal, healthcare, and individualized patient factors."[63] Pursuant to long-standing FDA policy, it is therefore the physician's decision whether to prescribe, based upon his or her medical judgment in light of each patient's individual circumstances at the time the prescription is written.

[59] 40 Fed. Reg. 15,392, 15,394 (Apr. 7, 1975).

[60] 37 Fed. Reg. 16,503, 16,504 (Aug. 15, 1972); 68 Fed. Reg. 6,062, 6,071 (Feb. 6, 2003).

[61] 21 C.F.R. § 202.1(e)(4)(ii)(c).

[62] FDA CDER, *MAPP 6700.1: Risk Management Activities in OND and ODS*, Manual of Policies and Procedures

[63] FDA, *Guidance for Industry, Development and Use of Risk Minimization Action Plans*, March 2005, March 2005, https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071616.pdf.

52. It may be appropriate to prescribe Actiq or Fentora outside of a cancer pain indication to address breakthrough pain in opioid-tolerant patients, depending on the acuity of pain, the onset of pain, the tolerance of the patient, and the effectiveness (or likely ineffectiveness) of other treatment options. That is, it is my opinion that these medicines, given their unique delivery system, may be appropriate for the appropriate patient with the appropriate pain profile, even outside cancer patients.[64]

53. My most successful use of Fentora to date was with a patient suffering from non-cancer-related low-back pain. He had been a participant in a clinical trial with Fentora and his symptoms responded remarkably well. In light of this success, we continued the medication post trial. The patient had five prior back surgeries and was on a fentanyl patch. However, he had difficulty tolerating and finding efficacy for breakthrough pain with the available short acting immediate release pain medications. He was working but finding it hard to get successfully through the workday. His pain started to affect his performance and resulted in several missed days from work. After starting on Fentora, he was able to deal more effectively with the breakthrough pain and his overall job performance improved. While stories like this may be dismissed by some as anecdotal, it is the clinical reality physicians see in everyday clinical practice. In medicine there are large variabilities in response of individual patients to different medications; that is why

[64] *See* "Statement from FDA Commissioner Scott Gottlieb, M.D. on the agency's 2019 policy and regulatory agenda for continued action to forcefully address the tragic epidemic of opioid abuse," news release, February 29, 2019, https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-agencys-2019-policy-and-regulatory-agenda-continued ("These products [TIRF products] are medically important for a specific group of patients experiencing breakthrough pain that may not be managed by their around-the-clock opioid pain medicine [...] The goal of the changes we will make to the TIRF REMS programs will be to make sure the program is working to mitigate the known risks of these medicines and that these drugs are being prescribed only to opioid-tolerant patients, and that those patients understand the risks and how to use TIRF medicines safely").

it is so important that clinicians individualize care and utilize the art as well as the science of medicine to most effectively care for patients.

F. Physicians Base Their Prescribing Decisions Upon Numerous Sources And Recognize That Some Research Is Supported By The Pharmaceutical Industry

54. Plaintiffs' experts inappropriately disregard valuable scientific evidence solely upon the basis of industry funding.[65] While industry funding can influence which topics are most heavily researched, such funding, by itself, does not invalidate findings. Physicians understand this dynamic and use such research, balanced alongside other sources of information, in making their clinical determinations and prescribing decisions.

55. Thinking critically about information is an important component of the practice of medicine. In addition to being aware that certain studies are funded by industry, physicians critically assess these studies (with the funding status in mind) to determine whether they are credible. Research has shown that physicians often perceive industry-sponsored studies as less credible than non-sponsored studies even when they have the same academic rigor.[66] This critical evaluation even includes direct marketing (or

[65] For example, Dr. Perri refers to funding and sponsoring clinical research, guidelines, and continuing medical education as "tak[ing] advantage" of the medical community. Expert Report of Matthew Perri III, *In Re: National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019 ("Perri Report"), pp. 14, 36 ("Pharmaceutical marketers take advantage of the medical community's reliance on scientific evidence by not only providing science-based messages directly through their marketing, but also through funding and sponsoring clinical research, clinical practice guidelines, and continuing medical education [...] However, the ever-increasing volume of research and publications may contain commercial bias because of the prevalence of company-sponsored research for the drug under evaluation.").

[66] *See* Kesselheim, Aaron S. et al., "A Randomized Study of How Physicians Interpret Research Funding Disclosures," New England Journal of Medicine Vol. 367, No. 12 (2012): 1119-27, ("Physicians discriminate among trials of varying degrees of rigor, but industry sponsorship negatively influences their perception of methodologic quality and reduces their willingness to believe and act on trial findings, independently of the trial's quality); Lacasse, Jeffrey R and Jonathan Leo, "Knowledge of ghostwriting and financial conflicts-of-interest reduces the perceived credibility of biomedical research," *BMC Research Notes* Vol. 4, No. 27 (2011): 1-6, ("Hospital-based clinicians (n = 50) who read a fictional vignette describing an antidepressant study found

"detailing") from pharmaceutical representatives. While sales representatives have an obvious motivation to put their products in the best possible light, in my experience, physicians focus on the important safety information and clinical evidence this detailing can also provide, keeping in mind the source of this information and checking against other resources at their disposal. These resources include but are not limited to their own experience with the products, commonly known risks with medications such as Schedule II opioids, the FDA-approved full prescribing information in product labels, the Physician's Desk Reference, peer-reviewed publications and studies, and common sense.[67]

V. THE FDA HAS IMPOSED UNIQUE REQUIREMENTS TO ENSURE THE SAFE USE AND DISTRIBUTION OF ACTIQ AND FENTORA AND THAT PRESCRIBERS ARE AWARE OF THE RISKS AND INDICATIONS

A. Actiq and Fentora Have Long Been Subject To FDA-Approved Risk Mitigation Programs

56. Prior to 2007, risk plans were usually termed Risk Management Programs (RMP) or a Risk Minimization Action Plans (RiskMAP).[68] The FDA defines a RiskMAP as a "strategic safety program designed to meet specific *goals* and *objectives* in minimizing known risks of a product while preserving its benefits. A RiskMAP targets one or more safety-related health outcomes or goals and uses one or more *tools* to achieve those

this vignette much less credible when it was accompanied with the disclosure of multiple COI [conflicts-of-interest] (financial COI, KOL status, and ghostwriting) than when no COI was present").

[67] Plaintiffs' experts have recognized this point, explaining that "there are a lot" of factors that influence doctors to prescribe medicines. Deposition of David Cutler, Ph.D., *In Re: National Prescription Opiate Litigation* MDL No. 2804, United States District Court, Northern District of Ohio, Eastern Division, April 26, 2019, pp. 182-185.

[68] FDA, "FDA's Role in Managing Medication Risks."

goals."[69] Among other priorities, these programs ensure that doctors and patients are informed on the safe usage and handling of TIRF medications.

57. The Food and Drug Administration Amendments Act of 2007 gave the FDA the authority to require a Risk Evaluation and Mitigation Strategy (REMS) for specific medications or classes of medications when sufficient risk concerns existed.[70]

58. Upon their launch, both Actiq and Fentora were subject to separate risk plans, which were strengthened over time. In 2012, Actiq and Fentora became subject to a special FDA-mandated class-wide REMS specific to TIRF products, which superseded previous risk management plans and imposed even stricter requirements.[71]

1. Actiq RMP

59. Actiq was approved in 1998 with an RMP that guarded against accidental ingestion by children, improper patient selection, and diversion or abuse. The Actiq RMP mandated child-proof packaging, availability in multiple dose strengths, uniform per mg pricing to avoid incentives to purchase stronger doses than necessary, and prescribing directions.[72] The Actiq RMP also specified proper labeling, including boxed warnings, patient leaflets,

[69] FDA, *Guidance for Industry, Development and Use of Risk Minimization Action Plans*, March 2005, https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071616.pdf, p. 5 (emphasis in original).

[70] FDA, "FDA's Role in Managing Medication Risks."

[71] FDA, "Approved Risk Evaluation and Mitigation Strategies (REMS)," available at https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=60, accessed May 7, 2019; TIRF REMS Access, Frequently Asked Questions. I understand that in 2008, Cephalon (later acquired by Teva) admitted fault and paid restitution for violations of the False Claims Act related to marketing for Actiq in the period from January 2001 to October 2001. To the extent that Plaintiffs' experts allege specific marketing practices by Teva beyond the "strict limitations imposed by FDA," they relate to this earlier litigation and are inconsistent with my knowledge of post-2008 marketing for Actiq and Fentora. See the Kessler Report, pp. 200-210.

[72] Anesta Corporation and Abbott Laboratories, "Actiq Risk Management Program," November 4, 1998, TEVA_MDL_A_00564336-65, at 00564342–00564346.

and package inserts in line with Schedule II classification, the most restrictive FDA classification available.[73] Actiq's manufacturer was required to monitor for inappropriate prescriptions and adverse events while maintaining active communication with the FDA regarding these issues.[74] The Actiq RMP also required FDA approval of all marketing materials. I have reviewed the FDA approved marketing materials for Actiq and find that they provide a fair and balanced presentation of the risks and benefits of Actiq.[75]

60. Key elements of the RMP were communicated to medical professionals through dissemination of educational materials to licensing boards and professional associations.[76] For example, in connection with CME programs, program providers had to acknowledge that they were familiar with the Actiq and Fentora RMPs.[77] CMEs were funded by Cephalon through independent medical education grants. According to CME guidelines, these grants had to "be developed and conducted independently of Cephalon and must be objective, balanced and scientifically rigorous."[78] Only organizations could receive grants, and not individuals. Cephalon employees could not have any control over program content, and "the program provider must maintain full control over the content, including the development of slide sets, other presentation materials and enduring materials. Cephalon employees may not prepare slide scripts or slides for speakers, target points for emphasis, or otherwise attempt to influence the content of the program."[79]

[73] TEVA_MDL_A_00564336-65, at 00564346–00564351.

[74] TEVA_MDL_A_00564336-65, at 00564358–00564364.

[75] "Actiq Marketing Materials," TEVA_MDL_A_00695218-6810.

[76] TEVA_MDL_A_00564336-65, at 00564348–00564351.

[77] TEVA_MDL_A_06880639-55, at 06880654-55.

[78] TEVA_MDL_A_06880639-55, at 06880639.

[79] TEVA_MDL_A_06880639-55, at 06880641.

61. The Actiq RMP emphasized that the medication was contraindicated for opioid non-tolerant patients as well as for treating acute or postoperative pain.[80] Product packaging as well as a patient leaflet distributed with the medication reiterated the contraindications to prescribers, pharmacists and patients.[81] In order to educate the medical community about Actiq prior to and following the launch of the medication, Anesta Corporation and Abbott Laboratories engaged in educational outreach through speakers, medical journals and pharmacy newsletters.[82]

62. Child safety also featured prominently in the Actiq RMP. Actiq's multi-layer laminated foil packet achieved 99% effectiveness in the child resistance test protocol, well in excess of the 80% required by regulation.[83] Actiq's label included detailed instructions for the safe disposal of used and partially used medication such that any residual medication would not pose a threat.[84]

63. The Actiq RMP required the manufacturer to actively monitor for signs of diversion or abuse that would trigger interventions and modifications to the RMP to improve its effectiveness. One part of the program involved soliciting interviews with Actiq patients

[80] TEVA_MDL_A_00564336-65, at 00564342.

[81] TEVA_MDL_A_00564336-65, at 00564344, 00564347.

[82] TEVA_MDL_A_00564336-65, at 00564342. While Plaintiffs' complaint assumes that all speaker programs funded by industry are biased, false, and misleading, the Actiq RiskMAP actually mandated such "educational outreach" programs, with all content provided by the manufacturer after FDA approval, in order to "educate the pharmacist and enlist their assistance as gatekeepers" and "emphasize the three key safety messages." TEVA_MDL_A_00564336-65, at 00564353.

[83] TEVA_MDL_A_00564336-65, at 00564343.

[84] "Actiq Label, November 1998," pp. 11, 13-14, 28-29.

after they filled a prescription to assess whether they had received the proper counseling, dosing instructions, and safety equipment.[85]

2. Fentora RiskMAP

64. Fentora was approved in 2006, with a RiskMAP that Cephalon developed based on FDA's Guidance for Industry on the Development and Use of RiskMAPs. Fentora's RiskMAP was called the Solutions through Education, Communication, and Understanding Risk Minimization Excellence (SECURE) Program. The SECURE Program focused on minimizing three specific risks: (1) use of Fentora by opioid non-tolerant individuals; (2) misuse, abuse and diversion of Fentora; and (3) accidental exposure to Fentora.[86]

65. The SECURE Program sought to minimize the risk of use by opioid non-tolerant patients primarily through communication and educational messaging targeted at prescribing physicians, dispensing pharmacists and patients.[87] The SECURE Program defined opioid-tolerant patients as those taking at least 60 mg of oral morphine per day or equianalgesic amounts of other opioids for a week or longer.[88] Warnings aimed at educating physicians about this contraindication were included in initial product announcement materials and were reiterated through direct mailings and face-to-face visits by Cephalon field representatives.[89]

[85] TEVA_MDL_A_00564336-65, at 00564359.

[86] Cephalon, Inc., "Fentora RiskMAP," September 18, 2006, TEVA_MDL_A_00265075-425, at 00265081.

[87] TEVA_MDL_A_00265075-425, at 00265082.

[88] TEVA_MDL_A_00265075-425, at 00265082.

[89] TEVA_MDL_A_00265075-425, at 00265090.

66. The SECURE program also sought to minimize misuse, abuse and diversion of the medicine through ensuring the integrity of the supply chain, creating tools to "educate broadly," and promptly detecting diversion or abuse.[90] First, all parties handling or prescribing Fentora needed to be compliant with existing distribution controls and recordkeeping requirements for Schedule II medicines set by the DEA.[91] For example, Fentora prescriptions could not be refilled and a physician visit was required to receive a new supply of the medicine.[92]

67. To minimize the risks of unintended exposure, Fentora was distributed with the "most stringent of child-resistant packaging requirements," included reminder messages on the packaging, and required direct counseling of Fentora patients advising them of the risk posed to children.[93] Fentora packaging and informational materials included instructions on proper disposal of the medication.[94]

3. TIRF REMS Program

68. Since March 2012, Actiq and Fentora have been subject to the TIRF REMS Program, which delineates the procedures that prescribers, patients, and suppliers must follow to handle or access TIRF products. The goals of the TIRF REMS Access program are to "mitigate the risk of misuse, abuse, addiction, overdose, and serious complications due to

[90] TEVA_MDL_A_00265075-425, at 00265082.

[91] TEVA_MDL_A_00265075-425, at 00265104.

[92] TEVA_MDL_A_00265075-425, at 00265093.

[93] TEVA_MDL_A_00265075-425, at 00265084.

[94] TEVA_MDL_A_00265075-425, at 00265215.

medication errors."[95] To ensure appropriate use of TIRF medications, the program delineates four goals: (1) "prescribing and dispensing TIRF medicines only to appropriate patients, which includes use only in opioid-tolerant patients;"[96] (2) "preventing inappropriate conversion between TIRF medicines;"[97] (3) "preventing accidental exposure to children and others for whom it was not prescribed;"[98] and (4) "educating prescribers, pharmacists, and patients on the potential for misuse, abuse, addiction, and overdose of TIRF medicines."[99]

69. The development and implementation of the TIRF REMS program incorporated many of the principles and objectives of the Actiq RMP and Fentora RiskMAP.[100] Healthcare providers prescribing TIRF medicines in an outpatient setting are required to review the prescriber educational materials and enroll in the TIRF REMS access program by completing and signing a Prescriber Enrollment Form, thus committing to comply with the program requirements.[101] Furthermore, physicians must meet with each patient to whom they will prescribe a TIRF product and review the benefits and risks as well as how to safely store and dispose of their medication. Before a TIRF product can be

[95] "Actiq TIRF REMS Documentation," TEVA_MDL_A_00709777-10056 at 00709810; "Fentora TIRF REMS Documentation," TEVA_MDL_A_00710057-205 at 00710077.

[96] TEVA_MDL_A_00709777-10056 at 00709810; TEVA_MDL_A_00710057-205 at 00710077.

[97] TEVA_MDL_A_00709777-10056 at 00709810; TEVA_MDL_A_00710057-205 at 00710077.

[98] TEVA_MDL_A_00709777-10056 at 00709810; TEVA_MDL_A_00710057-205 at 00710077.

[99] TEVA_MDL_A_00709777-10056 at 00709810; TEVA_MDL_A_00710057-205 at 00710077.

[100] FDA, "Standardizing and Evaluating Risk Evaluation and Mitigation Strategies."

[101] TIRF REMS Access, "Prescriber Enrollment Form," available at https://www.tirfremsaccess.com/TirfUI/rems/pdf/prescriber-enrollment-form.pdf; TEVA_MDL_A_00709777-10056 at 00709810; TIRF REMS Access, Frequently Asked Questions.

dispensed, every patient and prescriber must sign a Patient-Prescriber Agreement Form attesting that they reviewed this information.[102]

70. Enrollment is also required for all participants in the TIRF distribution chain, including wholesalers and distributors.[103] These parties are required to train relevant staff on the procedures and requirements of the TIRF REMS program and to distribute TIRF medicines only to enrolled pharmacies.[104] The TIRF REMS program also mandates that wholesalers and distributors provide complete data on inventory of TIRF medicines and shipments to enrolled pharmacies.[105] The wholesaler or distributor must agree to comply with periodic audits to ensure program compliance.[106]

71. Pharmacies must be enrolled in the TIRF REMS program to be eligible to receive shipments of TIRF products.[107] Both inpatient and outpatient pharmacies are required to enroll and train their staff in the proper usage and handling of TIRF medicines. Pharmacies are prohibited from lending, selling or transferring TIRF medications to any

[102] TIRF REMS Access, Frequently Asked Questions.

[103] TIRF REMS Access, Frequently Asked Questions, p. 12 ("Does a distributor have to enroll in the TIRF REMS Access program? Yes, distributors will need to enroll in the TIRF REMS Access program in order to be able to purchase and distribute TIRF medicines.").

[104] TEVA_MDL_A_00709777-10056 at 00709820 ("The Wholesaler/Distributor will ensure that relevant staff are trained on the TIRF REMS Access program procedures and will follow the requirements of the TIRF REMS Access program").

[105] TEVA_MDL_A_00709777-10056 at 00709820 ("The Wholesaler/Distributor will provide complete, unblinded and unblocked data (i.e. EDI 867 transmission) to the TIRF REMS Access program including information on shipments to enrolled pharmacies").

[106] TEVA_MDL_A_00709777-10056 at 00709820 ("The Wholesaler/Distributor will cooperate with periodic audits or non-compliance investigations to ensure that TIRF medicines are distributed in accordance with the program requirements").

[107] TIRF REMS Access, Frequently Asked Questions, p. 6 ("There are 3 types of outpatient pharmacies. They are all required to be enrolled in the TIRF REMS Access program, complete the TIRF REMS Education Program, and verify patient and prescriber enrollment when processing prescriptions.").

other pharmacy, institution, distributor or supplier.[108] Furthermore, all registered pharmacies must obtain TIRF medicines only from wholesalers and distributors enrolled in the TIRF REMS Access program.[109]

72. The maker of the TIRF medicine, or "TIRF Sponsor," is responsible for monitoring and ensuring compliance with the TIRF REMS Access program throughout the entire supply chain, from distribution through to the patient.[110] The TIRF Sponsor maintains a database of all enrolled parties. Given that all TIRF REMS participants—including patients, prescribers, distributors/wholesalers, and pharmacies—must re-enroll every two years, the TIRF Sponsor tracks the status of each party as either active or inactive.[111] The TIRF Sponsor uses these data in conjunction with distribution and prescription data to ensure that only actively enrolled distributors supply actively enrolled pharmacies, only actively enrolled healthcare providers prescribe TIRF medicines in an outpatient setting, and only actively enrolled patients receive TIRF medicines for outpatient use from actively enrolled pharmacies.

73. Following approval of the TIRF REMS program, each TIRF Sponsor is required to submit REMS Assessments to the FDA at six and twelve months following approval, and each year thereafter.[112] These reports include outreach statistics, utilization statistics, program infrastructure metrics, and safety surveillance reports. REMS Assessments done at 12 and 24 months following the TIRF REMS Access program approval also include

[108] TEVA_MDL_A_00709777-10056 at 00709817.

[109] TEVA_MDL_A_00709777-10056 at 00709815–00709818; TIRF REMS Access, Frequently Asked Questions.

[110] TEVA_MDL_A_00709777-10056 at 00709819–00709820.

[111] TEVA_MDL_A_00709777-10056 at 00709820.

[112] TEVA_MDL_A_00709777-10056 at 00709821.

surveys of patients, healthcare providers, and pharmacies. For each reporting period, outreach statistics measure the number of educational letters sent to prescribers and pharmacists, as well as the number of returned mailings.[113] Utilization statistics provide per-period and cumulative counts of enrolled patients, prescribers, pharmacies and distributors, as well as prescriptions authorized and prescriptions denied.[114] Program infrastructure metrics provide indications of how well the system is functioning, including information such as the number of inadvertent enrollment deactivations.[115] Safety surveillance includes ongoing monitoring of the FDA's Adverse Event Reporting System and other external databases for TIRF-medicine-related death, overdose, misuse, abuse, addiction, inappropriate prescribing, medication errors, and accidental exposures/ingestion.[116]

74. TIRF Sponsors are required by law to process and report to the FDA any adverse events related to their products.[117] Periodic surveys assess knowledge, attitude and behavior of prescribers, pharmacists and patients enrolled in the program.[118] Since its inception, the TIRF REMS program has been updated several times in order to reflect the current best practices of prescription opioid control.[119]

[113] TEVA_MDL_A_00709777-10056 at 00709779.

[114] TEVA_MDL_A_00709777-10056 at 00709779–00709780.

[115] TEVA_MDL_A_00709777-10056 at 00709780.

[116] TEVA_MDL_A_00709777-10056 at 00709781.

[117] TEVA_MDL_A_00709777-10056 at 00709781.

[118] TEVA_MDL_A_00709777-10056 at 00709781.

[119] FDA, "FDA Approved Drug Products, Fentora," available at https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021947, accessed February 19, 2019.

B. The TIRF REMS Program Ensures Prescribers Are Informed About the Risks, Indications, and Protocols for Safe Use of Actiq and Fentora

75. The TIRF REMS includes many measures intended to educate prescribers about the unique requirements for safe outpatient use of TIRF medications. These include prescriber enrollment, a knowledge assessment, a patient-prescriber agreement form, and direct outreach to licensed healthcare providers. These measures ensure that prescribers are aware of the risks, indications, and protocols for safe use of Actiq and Fentora. Notably, physicians prescribing Actiq or Fentora for inpatient use are not subject to the requirements of the TIRF REMS Access program.[120] In the inpatient setting, the best judgment of and consistent monitoring by the healthcare provider is sufficient to address the risks associated with TIRF medicines, but an authorized pharmacist must enroll the inpatient pharmacy itself in the TIRF REMS program, including reviewing the TIRF REMS ACCESS Education Program.[121]

76. Prescriber enrollment is required to ensure that prescribers understand the risks, indications, and safe use of TIRF medicines, and can demonstrate their understanding of how to mitigate the risks.[122] Each prescriber must review the Education Program, successfully complete the Knowledge Assessment, complete a Prescriber Enrollment form either online or via fax, and enter into a Patient-Prescriber Agreement.[123]

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[120] TIRF REMS Access, "Education Program for Prescribers and Pharmacists," p. 2.

[121] TEVA_MDL_A_00709777-10056, at 00709816 ("Inpatient Pharmacies: The authorized pharmacist must complete the following requirements to successfully enroll their inpatient pharmacy: i. Review the TIRF REMS Access Education Program (TIRF REMS Access Education Program) and successfully complete the pharmacy Knowledge Assessment.").

[122] TEVA_MDL_A_00709777-10056 at 00709810–00709813; TEVA_MDL_A_00710057-205 at 00710077–00710080.

[123] TEVA_MDL_A_00709777-10056 at 00709810, 00709826–00709851; TEVA_MDL_A_00710057-205 at 00710077, 00710097–00710122.

77. The Education Program provides guidance on identifying appropriate patients, as well as dosing, conversion, contraindications, use, storage, and disposal of TIRF medicines.[124] The Education Program provides specific thresholds at which a patient is considered opioid tolerant.[125] Contraindications include use by opioid non-tolerant patients, management of acute or postoperative pain such as migraine or dental pain, and use by patients with a known intolerance or hypersensitivity to any component in the medication.[126] Notably, the Education Program's guidance on appropriate patient selection does not list treatment of non-cancer pain as a contraindication.

78. The Education Program informs prescribers on proper assessment of patient-specific risk factors. Prescribers are asked to consider the patient's past or current alcohol or drug abuse, history of psychiatric illness, and family history of drug and alcohol abuse.[127] The program advises that "[c]oncerns about abuse and addiction should not prevent the proper management of pain."[128] Even in patients without additional risk factors, prescribers are advised that "all patients treated with opioids require careful monitoring for signs of abuse and addiction."[129] To limit the possibility of abuse, the Education Program emphasizes "proper assessment of patients; safe prescribing practices; periodic re-evaluation of therapy; proper dispensing and storage; keeping detailed records of

[124] TIRF REMS Access, "Education Program for Prescribers and Pharmacists"; TEVA_MDL_A_00709777-10056 at 00709826–00709847; TEVA_MDL_A_00710057-205 at 00710097–00710118.

[125] TIRF REMS Access, "Education Program for Prescribers and Pharmacists," p. 3.

[126] TIRF REMS Access, "Education Program for Prescribers and Pharmacists," p. 3.

[127] TIRF REMS Access, "Education Program for Prescribers and Pharmacists," p. 4.

[128] TIRF REMS Access, "Education Program for Prescribers and Pharmacists," p. 4.

[129] TIRF REMS Access, "Education Program for Prescribers and Pharmacists," p. 4.

prescribing information … and informing patients/caregivers to protect against theft and misuse of TIRF medicines."[130]

79. The Knowledge Assessment tests the prescriber's understanding of information presented in the Education Program. Successful completion is required for prescribers, pharmacies, and distributors to enroll in the TIRF REMS Access program.[131]

80. By enrolling in the program, the prescriber attests to compliance with all program requirements. These include reviewing full prescribing information for each TIRF medicine and completing the knowledge assessment. The prescriber further attests to understanding of risks and benefits; understanding potential for abuse; understanding indications and contraindications; understanding dosing and conversion between TIRF medications; providing Medication Guide for particular TIRF medicine to patient and reviewing it with them; and agreeing to follow-up visits to assess appropriateness of dose and signs of misuse and abuse.[132] The enrolling prescriber must provide a state license number, DEA number, and National Provider Identifier (NPI). Enrollment is effective for two years, after which time the prescriber must re-enroll to continue prescribing TIRF medicines.[133]

[130] TIRF REMS Access, "Education Program for Prescribers and Pharmacists," p. 4.

[131] TIRF REMS Access, Knowledge Assessment; TEVA_MDL_A_00709777-10056 at 00709848–00709851; TEVA_MDL_A_00710057-205 at 00710119–00710122.

[132] TIRF REMS Access, "Prescriber Enrollment Form"; TEVA_MDL_A_00709777-10056 at 00709852–00709854; TEVA_MDL_A_00710057-205 at 00710123–00710126.

[133] TEVA_MDL_A_00709777-10056 at 00709813; TEVA_MDL_A_00710057-205 at 00710080.

81. The prescriber is also required to complete the Patient-Prescriber Agreement Form ("PPAF") along with the patient.[134] The prescriber is required to provide a copy to the patient, retain a copy, and submit a copy to the TIRF REMS Access program within 10 days.[135] By signing the form, the prescriber attests to understanding indications and contraindications of TIRF medicines including an understanding of the definition of an opioid-tolerant patient. The prescriber further attests to providing and reviewing the appropriate Medication Guide with the patient; providing and reviewing the appropriate Medication Guide with the patient if the patient is changed to a different TIRF medicine; understanding that changes to a different TIRF medicines require starting all patients at lowest dose. Lastly, the prescriber attests to having counseled the patient regarding risks, benefits, appropriate use, and safety concerns specific to TIRF medicines. Both the prescriber and the patient must sign the PPAF before the prescription may be given.

82. Prior to implementation of the Program, "Dear Healthcare Provider" letters were sent to appropriately licensed healthcare professionals who may prescribe TIRF medicines, educating them on the risks of TIRF medicines and explaining that they must enroll in the Program to prescribe TIRF medicines. Per the FDA-approved TIRF REMS, Teva was obligated to discuss Actiq and Fentora with "pain management specialists (comprised of anesthesiologists, physical medicine and rehabilitation physicians), primary care physicians, oncologists, oncology nurse practitioners who treat breakthrough pain in patients with cancer, and other appropriately licensed healthcare professionals who

[134] TIRF REMS Access, Patient-Prescriber Agreement Form; TEVA_MDL_A_00709777-10056 at 00709855–00709857; TEVA_MDL_A_00710057-205 at 00710127–00710129.

[135] TEVA_MDL_A_00709777-10056 at 00709852.

prescribe TIRF medicines."[136] As a result, the FDA expressly recognized that non-oncologists could and would continue to write prescriptions for Actiq, Fentora, and other TIRF medicines for their patients.

83. Given these requirements, prescribers should have been aware of the risks, indications, and protocols for safe use of Actiq and Fentora before writing any prescription, as even Plaintiffs' experts acknowledge.[137]

[136] TEVA_MDL_A_00709777-10056, at 00709814 ("TIRF Sponsors will: [...] Ensure that prior to the first availability of the TIRF REMS Access program/website, Dear Healthcare Provider Letters will be sent. The target audience for the letters will include pain management specialists (comprised of anesthesiologists, physical medicine and rehabilitation physicians), primary care physicians, oncologists, oncology nurse practitioners who treat breakthrough pain in patients with cancer, and other appropriately licensed healthcare professionals who prescribe TIRF medicines. The letter will include information on the risks associated with the use of TIRF medicines and will explain to healthcare providers that if they wish to treat patients using TIRF medicines, they must enroll in the TIRF REMS Access program."). An example of one of these letters is available at TEVA_MDL_A_00970847-50.

The Actiq RMP similarly identifies the target audience for education and detailing about Actiq as "oncologists and pain management specialists." TEVA_MDL_A_00564336-365, at 00564352.

[137] Deposition of David S. Egilman MD, MPH, *In Re: National Prescription Opiate Litigation* MDL No. 2804, United States District Court, Northern District of Ohio, Eastern Division, April 25, 2019 ("Egilman Deposition"), pp. 201-203 ("Q. Are you aware, sir, that before a prescription can be written under the TIRF REMS program, a prescriber must sign an agreement with the patient stating that he or she has counseled the patient about the risk, benefits, and appropriate use of TIRF medicines?

A. That's what they're supposed to do, that's right.

Q. And are you aware that under the TIRF REMS program, prescribers must be aware of the risks of any TIRF REM -- TIRF medicine before they write a prescription for one of those medicines?

A. That's generally true under any program, yes.

Q. And are you aware under the TIRF REMS program, a doctor must agree to assess his or her patient for signs of misuse or abuse?

A. Yes.");
See also, "Deposition of Matthew Perri III," p. 565 ("Q. So these are requirements that are specific to this class of medications, is that correct?

A. Well, these requirements -- yes, I agree, they are specific to Actiq and this class of drugs. They are not unique in terms of REMS. There are other programs that pharmacists and doctors have to enroll, but this is certainly unique to the other opioids.").

C. The TIRF REMS Program Ensures That Patient Are Informed About the Risks, Indications, and Protocols for Safe Use of Actiq and Fentora

84. Patients must also understand the risks and benefits of the medicine and sign a PPAF with their healthcare provider to receive TIRF medicines for outpatient use.[138]

85. The patient is required to complete the PPAF along with the prescriber.[139] Each party completes their respective section and signs the document. The patient attests to receiving a copy of the appropriate Medication Guide and reviewing with prescriber. The Medication Guide is part of the product label that is approved by the FDA, and is specifically written to communicate with patients in lay terms. In particular, the Medication Guide includes specific risk disclosures with respect to opioids.[140] The patient must acknowledge that they understand the need for opioid-tolerance when taking TIRF medicines, and that they must stop taking TIRF medicines if they stop taking around-the-clock opioids. The patient attests to understanding how to take TIRF medicines, including dose and timing; understanding side effects; agreeing to contact their prescriber if the TIRF medicine does not relieve pain and to not change their dosage or take more often than directed. The patient agrees never to give away their TIRF medicines, to store the medicine safely, and to dispose of unused or unneeded TIRF medicines properly. The patient acknowledges that selling or giving away TIRF medicines is illegal. Both prescriber and patient must sign the PPAF before the

[138] TEVA_MDL_A_00709777-10056 at 00709812–00709813; TEVA_MDL_A_00710057-205 at 00710079–00710080.

[139] TIRF REMS Access, Frequently Asked Questions, p. 5 ("As a patient, how do I participate in the TIRF REMS Access program? You must sign a Patient-Prescriber Agreement with your prescriber and take your prescription for a TIRF medicine to an "enrolled" pharmacy. The pharmacy will enroll you in the TIRF REMS Access program. Your prescriber will go over important information you need to know before you take the TIRF medicine."); TIRF REMS Access, Patient-Prescriber Agreement Form.

[140] TEVA_MDL_A_00709793-802; TEVA_MDL_A_00710070-075.

prescription is given. The patient is given a copy of the PPAF for their records. As with the prescriber, a new PPAF must be completed every two years in order for a patient to continue receiving prescriptions for TIRF medicines.[141]

86. Patients are enrolled in the TIRF REMS Access program by the pharmacy at the time their first prescription is filled.[142]

87. Patients remain active until a trigger for inactivation occurs. Triggers include (a) passage of a six-month period in which the patient does not fill a prescription; and (b) the patient receiving prescriptions for TIRF medicines from multiple prescribers within an overlapping time frame.[143] Receiving prescriptions from multiple prescribers is suggestive of misuse, abuse, or addiction. A patient may have more than one current prescriber (e.g., a pain management specialist and a primary care physician) if prescriptions for TIRF medicines are not for the same or overlapping period of treatment.[144]

VI. IT IS INCORRECT TO ASSUME THAT ALL PROMOTION OF OPIOID MEDICINES, INCLUDING MARKETING MATERIALS INVOLVING ACTIQ AND FENTORA, IS FALSE OR MISLEADING

88. Plaintiffs' experts assume that all marketing of prescription opioids is false.[145] This assumption is not true, and ignores the role marketing can play as one of many sources of

[141] TEVA_MDL_A_00709777-10056 at 00709813.

[142] TEVA_MDL_A_00709777-10056 at 00709819; TEVA_MDL_A_00710057-205 at 00710087.

[143] TEVA_MDL_A_00709777-10056 at 00709819.

[144] TEVA_MDL_A_00709777-10056 at 00709819.

[145] Expert Report of Professor Meredith Rosenthal, *In Re: National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019 ("Rosenthal Report"), p. 50 ("I have been instructed by counsel to assume in my but-for scenarios that the fact finder (judge or jury) finds that all or virtually all promotion by the manufacturer Defendants from 1995 to the present was unlawful."); Perri Report, p. 138 ("I was asked to assume that the Plaintiffs' expert reports rendered in this case assessed the common messages delivered by the Defendants'

information that keep physicians up-to-date on the latest available treatment options. The marketing of opioids was certainly not misleading or deceptive in all cases, despite what Plaintiffs' experts assume.

89. In my experience, detailing can be informative. While I have never relied upon the information from sales representatives to make a prescribing decision, detailing has provided useful information about available treatments such as studies, full labels approved by the FDA, and other information about approved indications and potential side effects. Some detailing is the result of FDA requirements for educating physicians about the risks of new medicines, as was the case with the Actiq RiskMAP's "educational outreach" program.[146]

90. I have reviewed marketing materials produced by the Teva Defendants,[147] and I found them to be balanced and reasonable. They often include the full, FDA-approved label and risk information.[148] In my professional opinion, these marketing materials are not false or misleading when considered in context, and, in my opinion, they would not cause a prescriber to write an opioid prescription that was medically inappropriate or unnecessary. The repetition of the dangers and warnings of the potency of the medication

marketing and hold the opinions that Defendants' messages were false, misleading, inaccurate, or designed to misstate the risks and benefits of Defendants' drugs.").

[146] TEVA_MDL_A_00564336-65, at 00564353.

[147] "Actiq Marketing Materials," TEVA_MDL_A_00695218-6810; "Fentora Marketing Materials," TEVA_MDL_A_00025238-33471

[148] See, e.g. TEVA_MDL_A_00695218-6810, at 00695884-00695900, 00696492-00696506; TEVA_MDL_A_00025238-33471, at 00025873-00025876.

and its abuse potential sends a very clear signal that it is crucial to prescribe to the right individual.[149]

91. Despite Plaintiffs' expert Dr. Schumacher's broad claims about "widespread promotion and marketing of opioids by Defendants," defined to include the Teva and Actavis Generic Defendants,[150] Dr. Schumacher admitted that "[i]n the preparation of my report, I did not review any marketing materials from Teva," and that he had no evidence of any false marketing by the Teva or Actavis Generic Defendants.[151] Plaintiffs' expert Dr. Lembke includes an appendix to her report listing "Misleading Promotional Messages" from several Defendants, but notably includes none from Teva or the Actavis Generic Defendants.[152] Likewise, Dr. Perri testified that he is not offering any Teva USA- or Cephalon-specific opinion in his testimony and was relying upon other experts to assess whether any messages were false or misleading.[153]

[149] See, e.g. TEVA_MDL_A_00695218-6810, at 00696155 ("Important: Do not use FENTORA unless you are regularly using another opioid pain medicine around-the-clock for your cancer pain and your body is used to these medicines[…] Get emergency help right away if: […] an adult who has not been prescribed FENTORA uses it […] These are medical emergencies that can cause death."); TEVA_MDL_A_00695218-6810 at 00695619, ("ACTIQ contains fentanyl, an opioid agonist and a Schedule II controlled substance…Schedule II opioid substances…have the highest potential for abuse and risk of fatal overdose due to respiratory depression…This product must not be used in opioid non-tolerant patients.").

[150] Expert Report of Mark A. Schumacher, M.D., Ph.D., *In Re: National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019 ("Schumacher Report"), p. 6.

[151] Deposition of Mark A. Schumacher, M.D., Ph.D., *In Re: National Prescription Opiate Litigation* MDL No. 2804, United States District Court for the Northern District of Ohio, Eastern Division, April 23, 2019 ("Deposition of Mark A. Schumacher, M.D., Ph.D."), pp. 84, 102-105.

[152] Expert Report of Anna Lembke, M.D., *In Re: National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019 ("Lembke Report"), Appendix I.

[153] Deposition of Matthew Perri III, M.D., *In Re: National Prescription Opiate Litigation* MDL No. 2804, United States District Court for the Northern District of Ohio, Eastern Division, April 24, 2019 ("Deposition of Matthew Perri III"), pp. 420, 561.

92. Plaintiffs' experts identify several third-party studies funded by Cephalon or Teva, that upon my review, are not misleading.[154] The funding sources are clearly acknowledged, allowing readers to use their own medical judgment to decide on the merits of the studies.

93. Similarly, I have reviewed the third-party unbranded materials cited by Plaintiffs in their pleadings[155] from third-party organizations and parties identified as having received funding from Cephalon and Teva USA.[156] When taken in their entirety, these publications are fair and balanced in their presentation of the risks and benefits of opioid medications generally, and, in my opinion, they would not mislead a licensed prescriber into writing a medically inappropriate or unnecessary opioid prescription. For example,

[154] See, e.g. Portenoy et al., "Prevalence and characteristics of breakthrough pain in opioid-treated patients with chronic noncancer pain," *The Journal of Pain* Vol. 7, No. 8 (2006): 583-91, p. 583 ("Supported by a grant from Cephalon, Inc, West Chester, Pa. Cephalon has provided an unrestricted grant to Dr. Portenoy's department, and he has recently become a consultant to the company; he was not a paid consultant at the time that this study was conducted. Drs. Simon, Brennan, Taylor, and Shoemaker are consultants to Cephalon and are on the Speaker's Bureau for Cephalon."); Taylor et al., "Impact of breakthrough pain on quality of life in patients with chronic, noncancer pain: Patient perceptions and effect of treatment with oral transmucosal fentanyl citrate (OTFC®, ACTIQ®)," *Pain Medicine* Vol. 8, No. 3 (2007): 281-88, p. 287 ("This study was supported by a grant from Cephalon, Inc., West Chester, Pennsylvania."); Fine et al., "Long-term safety and tolerability of fentanyl buccal tablet for the treatment of breakthrough pain in opioid-tolerant patients with chronic pain: an 18-month study," *Journal of Pain and Symptom Management* Vol. 40, No. 5 (2010): 747-60, p. 747 ("The study was sponsored by Cephalon, Inc. At the request of the authors, writing support was provided by David Peters of Sequoia Medical Communications, Ltd., funded by Cephalon, Inc. Dr. Fine has served as an advisory board member and consultant for Cephalon, Inc. Dr. Rathmell has served as a medical advisory board member for Cephalon, Inc. Drs. Messina and Xie are employees of Cephalon, Inc.").

[155] Summit Third Amended Complaint, at ¶¶ 216, 217, 230, 238, 259, 270, 272, 282, 353, 376, 410-11, 416, 430. 431, 446.

[156] For a full list of documents considered, see Appendix B. These include American Pain Foundation, Treatment Options: A Guide for People Living with Pain; Bennett, Daniel S, "Breakthrough Pain: Treatment Rationale With Opioids," available at https://www.medscape.org/viewarticle/461612, accessed April 11, 2018; Brennan, Michael J., Steven D. Passik, and Kenneth L. Kirsh, "Pharmacologic Management of Breakthrough or Incident Pain," 2003. https://www.medscape.org/viewarticle/449803, accessed April 11, 2019; Cephalon, Inc., *Special Report: An Integrated Risk Evaluation and Mitigation Strategy for Fentanyl Buccal Tablet (Fentora) and Oral Transmucosal Fentanyl Citrate (Actiq)*, 2011; Fishman, Scott M., *Responsible Opioid Prescribing: A Physician's Guide* (Washington, DC: Waterford Life Sciences, 2007). Fine, Perry G., Christine Miaskowski, and Michael Brennan, *SELECT (Stratify, Examine, Listen, Evaluate, Control, Tailor): Opioid-Based Management of Persistent and Breakthrough Pain*, 2008; Cephalon, Inc., *Opioid Medications and REMS: A Patient's Guide*, 2010; Nalamachu, Srinivas et al., *Prescription Pain Medication: Preserving Patient Access While Curbing Abuse*, 2013; Webster, Lynn R. and M. Beth Dove, "Optimizing Opioid Treatment for Breakthrough Pain," 2007. www.medscape.org/viewarticle/563417, accessed October 10, 2017.

while Plaintiffs' experts critique a book by the Federation of State Medical Boards for "promoting the use of opioid painkillers"[157] and "reshaping the minds of prescribers,"[158] the book in question includes many warnings about safe opioid prescription.[159] Other materials cited by Plaintiffs' experts exhibit similar attention to both potential risks and utility of opioid treatment for chronic pain patients.[160]

94. Lastly, in my experience, manufacturers of generic medicines do not promote their products through in-person detailing or other paid marketing. At most, these generics manufacturers highlight the commercial availability of their products. Plaintiffs' expert

[157] Lembke Report, pp. 78-79 ("The Federation of State Medical Boards published a book promoting the use of opioid painkillers. This book was sponsored by a "consortium" that included Abbott Laboratories, Alpharma Pharmaceuticals, Cephalon, Inc., Endo Pharmaceuticals, the Wisconsin PPSG, and Purdue Pharma").

[158] Perri Report, p. 49 ("Fishman was a prominent KOL. The Fishman book was distributed to nearly 162,000 physicians and other prescribers through accredited CME. Reshaping the minds of prescribers through CPG development and associated distribution of these guidelines through educational (marketing) activities was an important aspect of Defendants marketing because of the impact it could have on sales").

[159] This is made clear within just the first ten pages. See, e.g. Fishman, Scott M., *Responsible Opioid Prescribing: A Physician's Guide* (Washington, DC: Waterford Life Sciences, 2007), p. 1 ("the fact that some patients will deceive a physician in order to obtain prescription opioids for non-medical use requires us to be vigilant when prescribing these potent and potentially abusable medications."); p. 2 ("Physicians cannot single-handedly eliminate the diversion and abuse of prescription opioids. *But we have a solemn responsibility – to our patients and to society – to be vigilant in reducing these risks.*" [Emphasis in original]); p. 5 ("[T]he combination of potential therapeutic benefit and high risk associated with opioid analgesics leaves us no alternative but to become more sophisticated risk managers. [...] We cannot ignore the potential risks associated with the use of controlled substances, including addiction."); pp. 6-8 (a section on the "Scope of the Problem," including statistics about abuse and overdose deaths).

[160] See, e.g. Chou, Roger et al., "Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain," *The Journal of Pain* Vol. 10, No. 2 (2009): 113-30. e22, p. 114 ("Clinicians and regulators must jointly seek a balanced approach to opioid use, acknowledging the legitimate medical need for opioids in some patients with CNCP, while concurrently recognizing the serious public health problem of abuse (see Glossary), addiction (see Glossary) and diversion (see Glossary), and implement procedures to reduce these risks"); p. 115-116 ("Proper patient selection is critical and requires a comprehensive benefit-to-harm evaluation that weighs the potential positive effects of opioids on pain and function against potential risks. Thorough risk assessment and stratification is appropriate in every case. This approach is justified by estimates of aberrant drug-related behaviors (see Glossary), drug abuse, or misuse in patients with CNCP, which range from 0% to 50%, depending on the population evaluated and methods used to define and identify these outcomes. [...] Implicit in the recommendation to conduct a comprehensive benefit-to-harm analysis is the recognition that an opioid trial may not be appropriate."); Noble M, Treadwell JR, Tregear SJ, et al. "Long-term opioid management for chronic noncancer pain." Cochrane Database Syst Rev. 2010;(1):CD006605, ("The findings of this systematic review suggest that proper management of a type of strong painkiller (opioids) in well-selected patients with no history of substance addiction or abuse can lead to long-term pain relief for some patients with a very small (though not zero) risk of developing addiction, abuse, or other serious side effects).

Dr. Perri agrees that generic manufacturers "generally don't [...] promote the safety, efficacy, or benefits of their generic medications."[161] So does Plaintiffs' expert Dr. Rosenthal.[162] I have seen no evidence, either cited in Plaintiffs' various expert reports or otherwise, to suggest that Teva USA or the Actavis Generic Defendants promoted their generic opioid medications with respect to those medications' safety or efficacy. At most, it appears that certain Actavis Generic Defendants engaged in limited "awareness" campaigns periodically, with respect to certain products, but those efforts to make prescribers aware that the medications were available did not contain discussion of their safety or efficacy.[163]

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[161] Deposition of Matthew Perri III, p. 547 ("Q. Okay. And generic manufacturers do not promote the safety efficacy, or benefits of their generic medications; is that correct?

A. I would agree that they generally don't do that [...] generally, I completely agree with this and this is what I see in the vast majority of the marketing messages associated with generics that I saw in the opioid matter, was that they focused on consistency of supply, pricing and quality of the products."); see also p. 554 ("[…] when we look at the overall balance for generics, we generally aren't going to see a lot of personal selling […]"); p. 555 ("Q. And if generic manufacturers were using sales representatives to put out that voice, that would affect their ability to offer those low prices; is that correct?
A. […] I don't know the inner workings of the generic manufacturers and what it would cost them to do that if they already have a sales force or if they don't. The ins and outs of that, my guess is it would cost them more money […]"); pp. 565-566 ("Q. Okay. Can we turn to Table II of your report? […] Table II is sort of your categorization of the marketing messages that you reviewed; is that correct?"
A. Yes.
Q. And as we discussed, these are not typically the type of marketing messages that generic manufacturers are going to be communicating, that these marketing messages would be more related to branded manufacturers; is that correct?
A. Yes, essentially that's correct.").

[162] Deposition of Meredith Rosenthal, *In Re: National Prescription Opiate Litigation* MDL No. 2804, United States District Court for the Northern District of Ohio, Eastern Division, May 4, 2019, pp. 197, 198 ("Generally, manufacturers will not detail physicians for generics. They may have other sales force activities that they do that relate to price, but individual physicians are not generally making a decision about one generic versus the other. That decision happens at the pharmacy level.").

[163] Andy Boyer, former Senior Vice President of Actavis Sales and Marketing and former head of Teva North America, testified that "[i]t is physically impossible for a generics company to hire enough sales representatives to go in and speak to physicians about all of [their] generics products." Deposition of Andrew Boyer ("Deposition of Andrew Boyer"), *In Re: National Prescription Opiate Litigation* MDL No. 2804, United States District Court for the Northern District of Ohio, Eastern Division, January 15, 2019, p. 317. He further added that "We don't detail products . . . These are not brands, these are generics. We offer up a price and we offer up a consistent supply in our supply chain and hopefully quality products . . . There's no pushing, there's no detailing, there's nothing else there." Deposition of Andrew Boyer, p. 346.

95. In short, Plaintiffs' assumption that all promotion (including all detailing) pertaining to opioids is false simply is untrue.

VII. CONCLUSION

96. Plaintiffs contend that prescribers were misled by allegedly false statements attributable to the Defendants about opioids. Plaintiffs do "not assert [...] that any specific prescription was caused by Defendants' deceptive marketing," yet also allege that "all prescriptions of opioids for chronic pain in the Bellwether Jurisdictions were written in reliance on [Defendants'] misrepresentations, omissions, and wrongdoing."[164] However, to my knowledge, none of Plaintiffs' experts has identified any false statements made by the Teva or Actavis Generic Defendants that caused any doctor in Ohio to write a harmful opioid prescription. In my professional experience, marketing regarding Actiq and Fentora did not cause me to prescribe opioids to any, much less all, of my opioid therapy patients. Physicians, myself included, critically assess a wide range of sources when making prescription decisions, and above all look at each specific patient's needs and circumstances.

97. Plaintiffs do not address how any prescriber who read the labels of Actiq and Fentora, was familiar with the Risk Management Programs for these medicines, or who was enrolled in the TIRF REMS program—with all the accompanying disclosures and requirements—could have been misled into writing a prescription of Actiq or Fentora. Plaintiffs allege that Defendants "deprived prescribers and patients of the ability to make informed choices about whether, when, and which opioids to prescribe and use, for how

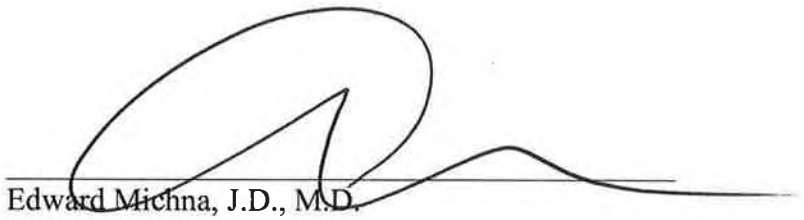
[164] Plaintiffs' Responses and Objections to Manufacturer Defendants' Fourth Set of Interrogatories, pp. 6-7.

long, and at what doses" through marketing, continuing education programs, and websites (among other media), yet ignore the central FDA-approved apparatus for ensuring that physicians, distributors, and patients all had access to full information about these TIRF products.

98. Taken together, the likelihood that any prescribers were misled about the risks associated with Actiq or Fentora or their FDA-approved indications is strictly limited by the detailed disclosures and affirmative patient and prescriber acknowledgments required by the relevant risk management programs to which Actiq and Fentora were subject since launch. Off-label prescribing by physicians is common and can be appropriate when physicians exercise their medical judgment based on individual patient's medical needs, circumstances, and preferences.

* * *

Signed on the 10th day of May, 2019.



Edward Michna, J.D., M.D.

Appendix A

Curriculum Vitae

HARVARD MEDICAL SCHOOL
CURRICULUM VITAE

Date Prepared: May 9, 2019

Name: Edward Michna

Office Address: Brigham and Women's Hospital
Department of Anesthesiology, Perioperative and Pain Medicine
75 Francis Street
Boston, MA 02115

Home Address: 62 Alba Road
Wellesley, MA 02481

Work Phone: (617) 732-6707

Work Email: emichna@partners.org

Work Fax: (617) 731-5453

Place of Birth: New Brunswick, NJ

Education:

1982	B.S.	Pharmacology	Rutgers College of Pharmacy, New Jersey
1985	J.D.	Law	Seton Hall Law School, New Jersey
1991	M.D.	Medicine	UMDNJ - New Jersey Medical School

Postdoctoral Training:

01/91-12/92	Internship	Medicine	Monmouth Medical Center, NJ
01/92-12/95	Resident	Anesthesia	Brigham & Women's Hospital, Boston, MA
01/95-12/96	Fellow	Pain	Brigham & Women's Hospital, Boston, MA

Faculty Academic Appointments:

1992-1996	Clinical Fellow	Anaesthesia	Harvard Medical School
1996-2009	Clinical Instructor	Anaesthesia	Harvard Medical School
2009-Present	Assistant Professor	Anaesthesia	Harvard Medical School

Appointments at Hospitals/Affiliated Institution:

01/96-12/97	Staff Anesthesiologist	Boston Medical Center
01/97-12/07	Staff Anesthesiologist	Massachusetts General Hospital
01/98-12/08	Staff Anesthesiologist	St. Elizabeth's Hospital

01/00-12/01	Staff Anesthesiologist	New England Medical Center
01/00-12/04	Consulting Staff, Anesthesia	Spaulding Rehabilitation Institute
01/01-12/04	Consulting Staff, Anesthesia	Youville Rehabilitation
01/96-present	Staff Anesthesiologist	Pain Management Center, BWH
01/97-present	Clinical Staff, Anesthesia	Dana-Farber Cancer Institute

Major Administrative Leadership Positions:

2001-2010	Director of Interventional Pain Management, Dana Farber Cancer Institute
2001	Associate Director of Pain Trials Center, Department of Anesthesia, Brigham and Women's Hospital
2002-present	Director of Pain Trials Center, Department of Anesthesia, Brigham and Women's Hospital

Committee Service:

Local:

1995-1997	Ethics Committee	Brigham and Women's Hospital
1998-2005	Quality Assurance Committee	Pain Management Center, BWH
1998-1999	Women's Health Advisory Group	Brigham and Women's Hospital
1998-1999	Operation Committee Group	Pain Management Center, BWH
2002-2004	Pain Committee	Brigham and Women's Hospital
2010-2012	Narcotic Advisory Committee for Establishing Hospital Guidelines	Boston Children’s Hospital

National

2009-	Drug Advisory Committee on Anesthesia and Analgesia, part time consultant Food and Drug Administration

Professional Societies:

1992-	Massachusetts Society of Anesthesiologists, Member	
1992-	American Society of Anesthesiology, Member	
	2002-Present	Adjuvant reviewer, Committee on Professional Liability
	2003-2004	Task force on Liability in Invasive Pain Management
	2008-	Committee on Expert Witness Testimony Review
1996-	American Pain Society, Member	
	2006-2008	Pain Care Coalition
	2008-2012	Chairman, Committee on Public Policy
	2009-2011	Chairman, Pain Care Coalition
	2012	Director-at-Large
1996-	American Medical Association, Member	

1996- International Association for the Study of Pain, Member
1998- New England Pain Association, Member
1999-2001 State Representative
2001-2001 Treasurer
2002-2003 President Elect
2003-2004 President
2004-2005 Past President
2004, 2005 Course Co-Director, Winter Conference
2005-2007 Treasurer
2006- American Academy of Pain Management, Member
2008- Committee on External Affairs
2009-2011 Committee on Nominations and Appointments
2009- Local Initiatives Committee, MA representative

Editorial Activities:

Ad Hoc Reviewer:

2008- Cancer
2008- Annals of Internal Medicine
2008- Medical Letter
2008- Pain Medicine

Honors and Prizes:

1978-1978 Rho Chi Achievement Award, Rutgers Pharmacy School
2007-2008 Mayday Pain and Society Fellowship: A Media and Policy Initiative, Mayday Society
2007 Teacher of the Year Award (Voted by the 2006-2007 Pain Management Fellows), Brigham and Women's Hospital
2012 Distinguished Service Award, American Pain Society
2013 Teacher of Year Award (Voted by 2012-2013 Pain Management Fellows), BWH

Report of Funded and Unfunded Projects:

Funding Information:

2008 A Website for the Self-Management of Chronic Back Pain, Phase II
U.S. Department of Health & Human Services / 2008P002096
Sub Investigator
The purpose is to evaluate the functionality of lower back pain patients on opiods.

2008 Ambulatory Data Recorder (ADR) Spinal Cord Stimulator Study
Medtronic, Inc / , 2008P001125
Sub Investigator

	The purpose is to evaluate the functionality and pain relief of spinal cord stimulation.
2008	Open-Label Extension, Single-Arm, Flexible-Dosing, Phase III Trial with CG5503 Extended-Release (ER) in Patients with Moderate to Severe Chronic Pain Johnson & Johnson, Inc. / 2007P001193 Principal Investigator This is a long term safety and efficacy study
2008	A Randomized, Double-Blind, Placebo-Controlled, Parallel-Group With a Crossover Confirmation Period Study of RWJ-333369 for the Treatment of Postherpetic Neuralgia Amendment INT-1 Johnson & Johnson, Inc. / 2007P000973 Principal Investigator The purpose is to show safety and efficacy.
2008	A Randomized, Double-Blind, Placebo-and Active-Control, Parallel-Arm, Phase III Trial with Controlled Adjustment of Dose to Evaluate the Efficacy and Safety of CG5503 Extended-Release (ER) in Subjects with Moderate to Severe Chronic Low Back Pain Johnson & Johnson, Inc. / 2007P000135 Principal Investigator This is a long term safety and efficacy study.
2008	A Randomized, Double-Blind, Active- and Placebo-Controlled, Parallel-Group, Multicenter Study to Evaluate the Efficacy and Safety of Multiple Doses of CG5503 Immediate-Release Formulation in the Treatment of Acute Pain From Total Hip Replacement Surgery Followed by a Voluntary Open-Label Extension Johnson & Johnson, Inc. / 2006P001813 Principal Investigator The purpose is to show safety and efficacy for FDA approval.
2008	A Multicenter, Open-labeled Study of the Long-term Safety and Efficacy of Lubiprostone in Patients with Opioid-induced Bowel Dysfunction Sucampo Phamrmaceuticals, Inc. / 2008P001739 Principal Investigator The purpose is to show safety and efficacy.
2008	A Double Blind, Randomized, Placebo Controlled, Parallel Group Dose-Range Exploration Study of Sativex® in Relieving Pain in Patients With Advanced Cancer, Who Experience Inadequate Analgesia During Optimized Chronic Opioid Therapy GW Pharma Ltd / 2007P002392 Principal Investigator The purpose is to show safety and efficacy.
2008	A Multicenter, Randomized, Placebo-Controlled, Double-Blinded Study of the Efficacy and Safety of Lubiprostone in Patients with Opioid-induced Bowel Dysfunction Sucampo Phamrmaceuticals, Inc / 2007P002124 Principal Investigator The purpose is to show safety and efficacy.

2008	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Subcutaneous MOA-728 for the Treatment of Opioid-Induced Constipation in Subjects with Chronic Non-Malignant Pain Wyeth Pharmaceuticals, Inc / 2007P001453 Principal Investigator The purpose is to show safety and efficacy.
2008	Intrathecal Therapy for Chronic Non-Cancer Pain: An Analysis of its Efficacy Departmental Funds / 2007P000874 Sub Investigator The purpose is to show safety and efficacy.
2008	A Multicenter, Randomized, Double-Blind, Placebo-Controlled, Parallel-Group Study of Oral MOA-728 for the Treatment of Opioid-Induced Bowel Dysfunction in Subjects with Chronic Non-Malignant Pain Wyeth Pharmaceuticals, Inc / 2006P001344 Principal Investigator The purpose is to show safety and efficacy.

Report of Local Teaching and Training:

Teaching of Students in Courses:

1998	Pharmacology Course Small group session on pain management	Tufts Medical School
1999-	Anesthesia Pain/Clinical 3rd year medical students	HMS 2-4 students/mo; Attending: ½ day
2002-	Elective Oncology/Palliative Care 4th year medical students	HMS 2-8 students/yr; Attending: ½ day
2007, 2008	Opioids for Chronic Pain 3rd year medical school class	HMS-MIT: HST

Formal Teaching of Peers:

2008	The Physician's Emotional Response to a Lawsuit Harvard Anesthesia Review and Update	Single presentation Boston
2005	Neuropathic Pain: A Practical Approach Harvard Continuing Education Course	Single presentation Boston

Local Invited Presentations:

1997	Reflex Sympathetic Dystrophy / Grand Rounds Brigham and Women's Hospital
1998, 1999	Pain Management / Grand Rounds

	Brigham and Women's Hospital
2000	Legal Aspects of Pain Management / Grand Rounds Massachusetts General Hospital
2000	Legal Aspects of General Medical Practice / Grand Rounds Brigham and Women's Hospital
2001	Implantable Pumps and Devices / Grand Rounds Harvard Medical School
2001	Neuropathic Pain / Grand Rounds Brigham and Women's Hospital
2001	Pain Management / Case Conference Brigham and Women's Hospital
2003	Broadening Your Perception of Pain Management / Grand Rounds Brigham and Women's Hospital
2004	Legal Aspects of Pain Medicine / Grand Rounds Massachusetts General Hospital
2004	Pelvic Pain / Grand Rounds Massachusetts General Hospital
2004	Legal Aspects of Pain Medicine, Broadening Your Perception of Pain Medicine Brigham and Women's Hospital Nursing and Pharmacy
2005	Legal Aspects of Pain Medicine / Grand Rounds Beth Israel Deaconess Medical Center
2007	Update on Legal issues in Pain Management / Grand Rounds Brigham and Women's Hospital

Regional, National, or International Contributions: Invited Presentations

Regional:

1999	Legal Aspects of Pain Management and Anesthesia St. Elizabeth's Hospital [Conference]
2001,2005,2007,2008	The Legal Aspects of Pain Management, Tufts Medical School New England Medical Center [Invited Lecture]
2003	Implementing the Guidelines for Opioid Therapy, Family Medicine Primary Care Update, Groton CT [Invited Lecture]
2004	Legal Aspects of Pain Medicine, Tufts Medical School New England Medical Center [Invited Lecture]
2006	Legal Aspects of Pain Medicine and Anesthesia. The 29th Annual Anesthesia Symposium, Baystate Medical Center [Invited Lecture]
2006	Legal Aspects of Pain and Anesthesia, Tufts Medical School New England Medical Center [Invited Lecture]
2006	Beyond Standards and Guidelines: Optimizing Access to Opioids, American Cancer Society [Invited Lecture]
2006	Guidelines for Prescribing Opioids for Chronic Pain: Effectiveness, Legalities, Addiction, New England Pain Society, Providence, Rhode Island [Invited Lecture]

2007	Legal Aspects of Pain Management, 60th Annual Meeting New England Assembly of Nurse Anesthetists, Burlington, MA [Invited Lecture]
2008	Medical Legal Issues in the Management of Chronic Pain, Rhode Island Internal Medicine Care Organization, Providence, RI [Invited Lecture]
2009	and the Law, Tufts Medical School, Master's Program in Pain [Invited Lecture]

National

2003	Management of a Chronic Low Back Pain Patient with Interventional Procedures and Medications, Annual Meeting of the American Society of Anesthesiologists [Problem Based Learning Discussion]
2005	What's New in Pain Management? Massachusetts Society of Anesthesia [Invited Speaker]
2005	Legal Aspects of Pain and Anesthesia, Massachusetts Society of Anesthesia [Invited Speaker]
2007	JCAHO Update on Sedation, Society of Interventional Radiology Annual Meeting, Seattle WA [Invited Lecture]
2007	Medical Legal Aspects of Prescribing Opioids, 15th Annual Scientific Meeting of the International Pelvic Pain Society, San Diego, CA
2008	Medicolegal aspects of sedating children-What is my liability as the supervising physician or administering nurse? Society of Interventional Radiology Annual Meeting, Washington D.C. [Invited Lecture]
2008	Opioids in Clinical Practice, 16th Annual Scientific Meeting of the International Pelvic Pain Society, Lake Buena Vista, FL [Invited Lecture]
2008	Workshop on Preparing for Depositions and Testimonies: Impact of a Lawsuit, Annual Meeting of the American Society of Anesthesiologists, San Diego, CA [Invited Lecture]
2008	Recent Legal Controversies Surrounding Opioids, American Academy of Pain Medicine 25th Annual Meeting, Honolulu, HI [Invited Lecture]
2009	What's my Liability: Medicolegal Aspects of Sedation, Society of Interventional Radiology Annual Meeting, San Diego, CA [Invited Lecture]
2009	Depositions and Testimony Workshop: The Anatomy of a Lawsuit, American Society of Anesthesiologists, Annual Meeting, New Orleans, LA [Invited Lecture]
2010	Pain Treatment at the Cervical Spinal Level: Emerging evidence from the ASA Closed Claim Study, American Academy of Pain Medicine 26th Annual Meeting, San Antonio, TX [Invited Lecture]
2010	Is the use of Sedation Safe During Neuraxial Interventions? American Academy of Pain Medicine 26th Annual Meeting, San Antonio, TX [Invited Lecture]
2010	Pain Medicine Litigation Practices through Mock Trial Review: Role of Defendant, American Academy of Pain Medicine 26th Annual Meeting, San Antonio, TX [Invited Lecture]

2010	Efficacy of Subcutaneous Methylnaltrexone In The Treatment Of Opioid Induced Constipation: A Responder Post Hoc Analysis. American Academy of Pain Medicine 26th Annual Meeting, San Antonio, TX [Poster Presentation]
2010	Subcutaneous Methylnaltrexone Treatment for Opioid-Induced Constipation: Effect On Pain And Opioid Withdrawal Symptoms. American Academy of Pain Medicine 26th Annual Meeting, San Antonio, TX [Poster Presentation]
2010	Workshop on Preparing for Depositions and Testimonies, Annual Meeting of the American Society of Anesthesiologists, San Diego, CA [Invited Lecture]
2011	Impact on Defendant of Being Sued: How to Survive and Succeed, Workshop: Malpractice Experience: Survival Skills for Defendants and Witnesses, Annual Meeting of the American Society of Anesthesiologists, Chicago, IL [Invited Lecture]
2011	What's My Liability: Medicolegal Aspects of Sedation, Panel: Sedation and the Anesthesiologist: Guidelines, Liability and Reimbursements, Annual Meeting of the American Society of Anesthesiologists, Chicago, IL [Invited Lecture]

International

2009	Update on Risk Evaluation and Mitigation Strategies Lecture-Opioids and the Law, Interventional Spinal Injection (ISIS) Meeting, Toronto, Canada [Invited Lecture]
2010	Cervical Injections-- Risk vs. Benefit: A Review of the ASA Closed Claims Data, 14th World Pain Clinic Congress & the 1st Asian Congress on Pain, Beijing, P.R. China **[Invited Lecture]**

Report of Clinical Activities and Innovations:

Licensure and Certification:

1982	Registered Pharmacist
1985	Member of New Jersey Bar
1995	Massachusetts Medical License
1997	California Medical License
1998	Diplomat of the American Board of Anesthesia
1998, 2009	Diplomat of the American Board of Anesthesia, Pain Medicine
2004	Diplomat of the American Board of Palliative Care

Practice Activities:

1996-	Anesthesia	BWH, Pain Management Ctr	30-40 patients/clinic day
2001-	Anesthesia	BWH, Pain Trials Ctr	12 trials any one time 40 patients/day

Report of Education of Patients and Service to the Community

Activities:

2002-2004	Board Member, Drug Utilization Review Board, Mass Health
2004-2005	Chair-Elect, Drug Utilization Review Board, Mass Health
2005-2006	Chairman, Drug Utilization Review Board, Mass Health
2006-2007	Board Member, Mass Health

Report of Scholarship

Peer-Reviewed Publications in print or other media:

1. Narang S, Wasan AD, Ross EL, **Michna E**, Chen JY, Jamison RN. Patients with chronic pain on opioid therapy taking dronabinol: incidence of false negatives using radioimmunoassay. J Opioid Management. 2008; 4(1):21-6.

2. Janfaza DR, **Michna E**, Pisini JV, Ross EL. Bedside implantation of a trial spinal cord stimulator for intractable anginal pain. Anesth Analg. 1998;87(6):1242-4.

3. Mason KP, **Michna E**, Zurakowski D, Koka B, Hickok SE, Burrows PE. Serum alcohol levels after ethanol embolization and sclerotherapy in children. Radiology. 2000;217(1):127-132.

4. Mason KP, **Michna E**, DiNardo JA, Zurakowski D, Karian VE, Connor L, Burrows PE. Evolution of a protocol for ketamine-induced sedation as an alternative to general anesthesia for interventional radiologic procedures in pediatric patients. . Radiol. 2002;225(2):457-65.

5. **Michna E**, Ross EL, Hynes WL, Nedeljkovic SS, Soumekh S, Janfaza D, Palombi D, Jamison RN. Predicting aberrant drug behavior in patients treated for chronic pain: importance of abuse history. J Pain Symptom Management. 2004;28(3):250-8.

6. Sanborn PA, **Michna E**, Zurakowski D, Burrows PE, Fontaine PJ, Connor L, Mason KP. Advserse Cardiovascular and Respiratory Events during Sedation of Pediatric Patients for Imaging Examinations. Radiology. 2005;237(1): 288-94.

7. Mason KP, **Michna E**, Zurakowski D, Burrows PE, Pirich MA, Carrier M, Fontaine PJ, Sethna NF. Value of bispectral index monitor in differentiating between moderate and deep Ramsay Sedation Scores in children. Paediatr Anaesth. 2006;16(12):1226-31.

8. **Michna E**, Jamison RN, Pham LD, Ross EL, Janfaza D, Nedeljkovic SS, Narang S, Palombi D, Wasan AD. Urine toxicology screening among chronic pain patients on opioid therapy: frequency and predictability of abnormal findings. Clin J Pain. 2007;23(2):173-9.

9. Jamison RN, Ross EL, Wasan AD, **Michna E.** Comment on Ballantyne and LaForge, Opioid dependence and addiction during opioid treatment of chronic pain. Pain 2007;129:235-55. Pain 2007;132(1-2):218-9.

10. Narang S, Wasan AD, Ross EL, **Michna E**, Chen JY, Jamison RN . Patients with chronic pain on opioid therapy taking dronabinol: incidence of false negatives using radioimmunoassay. Opioid Manag. 2008;4(1):21-6.

11. Narang S, Gibson D, Wasan AD, Ross EL, **Michna E**, Nedeljkovic SS, Jamison RN. Efficacy of dronabinol as an adjuvant treatment for chronic pain patients on opioid therapy. J Pain. 2008;9 (3):254-64.

12. Wasan AD, **Michna E**, Janfaza D, Greenfield S, Teter CJ, Jamison RN. Interpreting Urine Drug Tests: Prevalence of Morphine Metabolism to Hydromorphone in Chronic Pain Patients Treated with Morphine. Pain Med. 2008;9(7):918-23.

13. Jamison R, Wasan A, **Michna E**, Ross E, Chen L, Holcomb C, Edwards R. Substance abuse treatment for high risk chronic pain patients on opioid therapy. J Pain 2009; 10(4). DOI: 10.1016/j.jpain.2009.01.214

14. Jamison R, Wasan A, Edwards R, Chen L, Holcomb C, **Michna E**. Administration of opioids misuse screening tools: Does having a clinician-patient relationship make a difference in the way patients respond? J Pain 01/2009; 10(4). DOI: 10.1016/j.jpain.2009.01.041

15. Blonsky R, **Michna E**, Schulman S, Tzanis E, Manley A, Zhang H, Randazzo B. Subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with chronic non-malignant pain. Eur J Pain (London) 2009; 10(4). DOI: 10.1016/j.jpain.2009.01.277

16. Fitzgibbon DR, Rathmell JP, **Michna E**, Stephens LS, Posner KL, Domino KB. Malpractice claims associated with medication management for chronic pain. Anesthesiology. 2010;112(4):948-56.

17. **Michna E**, Duh M, Korves C, Dahl JL. Removal of Opioid/Acetaminophen Combination Prescription Pain Medications: Assessing the Evidence for Hepatotoxicity and Consequences of Removal of These Medications. Pain Med. 2010;11(3):369-78.

18. Jamison RN, Ross EL, **Michna E**, Chen LQ, Holcomb C, Wasan AD. Substance misuse treatment for high-risk chronic pain patients on opioid therapy: A randomized trial. Pain. 2010:150(3):390-400

19. Duh MS, Vekeman F, Korves C, Lefebvre P, Dial E, Latremouille-Viau D, Wei RS, Stangle BE, Lafeuille MH, **Michna E**, Greenberg PE. Risk of hepatotoxicity-related hospitalizations among patients treated with opioid/acetaminophen combination prescription pain medications. Pain Med. 2010;11(11):1718-25

20. Rathmell JP, **Michna E**, Fitzgibbon DR, Stephens LS, Posner KL, Domino KB. Injury and liability associated with cervical procedures for chronic pain. Anesthesiology. 2011;114(4):918-26.

21. **Michna E**, Blonsky ER, Schulman S, Tzanis E, Manley A, Zhang H, Iyer S, Randazzo B. Subcutaneous Methylnaltrexone for Treatment of Opioid-Induced Constipation in Patients With Chronic, Nonmalignant Pain: A Randomized Controlled Study. J Pain. 2011;12(5):554-62

22. Edwards RR, Wasan AD, **Michna E,** Greenbaum S, Ross E, Jamison RN. Elevated Pain Sensitivity in Chronic Pain Patients at Risk for Opioid Misuse. J Pain 2011; 12(9):953-963.

23. Jamison RN, Serraillier J, **Michna E.** Assessment and Treatment of Abuse Risk in Opioid Prescribing for Chronic Pain. Pain Research and Treatment 2011;941808.

24. **Michna E**, Weil AJ, Duerden M, Schulman S, Wang W, Tzanis E, Zhang H, Yu D, Manley A, Randazzo B. Efficacy of Subcutaneous Methylnaltrexone in the Treatment of Opioid-Induced Constipation: A Responder Post Hoc Analysis. Pain Med. 2011;12(8):1223-30.

25. Webster L, **Michna E**, Khan A, Israel R, Manley A, Zhang H, Maller E, Tzanis E. The long-term efficacy of subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with chronic nonmalignant pain. J Pain. 2011; 12(4). DOI: 10.1016/j.jpain.2011.02.283

26. Webster L, **Michna E**, Khan A, Israel R, Manley A, Zhang H, Tzanis E, Maller E. The long-term safety of subcutaneous methylnaltrexone for the treatment of opioid-induced constipation in patients with chronic nonmalignant pain. J Pain 2011; 12(4). DOI: 10.1016/j.jpain.2011.02.285 .

27. Wasan AD, Ross EL, **Michna E**, Chibnik L, Greenfield SF, Weiss RD, Jamison RN. Craving of prescription opioids in patients with chronic pain: a longitudinal outcomes trial. J Pain. 2012;13(2):146-54.

28. Turk DC, O'Connor AB, Dworkin RH, Chaudhry A, Katz NP, Adams EH, Brownstein JS, Comer SD, Dart R, Dasgupta N, Denisco RA, Klein M, Leiderman DB, Lubran R, Rappaport BA, Zacnym JP, Ahdieh H, Burke LB, Cowan P, Jacobs P, Malamut R, Markman J, **Michna E**, Palmer P, Peirce-Sandner S, Potter JS, Raja SN, Rauschkolb C, Roland CL, Webster LR, Weiss RD, Wolf K. Research design considerations for clinical studies of abuse-deterrent opioid analgesics: IMMPACT recommendations. Pain. 2012; 153(10):1997-2008.

29. Jamison RN, Edwards RR, Liu X, Ross EL, **Michna E**., Warnick M, Wasan AD. Relationship of Negative Affect and Outcome of an Opioid Therapy Trial Among Low Back Pain Patients. Pain Pract. 2013;13(3):173-81.

30. **Michna E**, Cheng WY, Korves C, Birnbaum H, Andrews R, Zhou Z, Joshi AV, Schaaf D, Mardekian J, Sheng M. Systematic literature review and meta-analysis of the efficacy and safety of prescription opioids, including abuse-deterrent formulations, in non-cancer pain management. Pain Med. 2014; 15(1):79-92.

31. Issa MA, Narang S, Jamison RN, **Michna E**, Edwards RR, Penetar DM, Wasan AD. The subjective psychoactive effects of oral dronabinol studied in a randomized controlled crossover clinical trial for pain. Clin J Pain. 2014; 30(6):472-478.

32. Rossiter LF, Kirson NY, Shei A, White AG, Birnbaum HG, Ben-Joseph R, **Michna E**. J Med Econ. 2014; 17(4):279-287.

33. **Michna E**, Kirson NY, Shei A, Birnbaum HG, Ben-Joseph R. Use of prescription opioids with abuse-deterrent technology to address opioid abuse. Curr Med Res Opin. 2014; 30(8):1589-1598.

34. Kirson NY, Shei A, White AG, Birnbaum HG, Ben-Joseph R, Rossiter LF, **Michna E**. Societal economic benefits associated with an extended-release opioid with abuse-deterrent technology in the United States. Pain Med. 2014; Jul 8. Doi: 10.1111/pme.12489. PMID: 25041231.

35. Kirson N, **Michna E**, Rossiter L et al. Medical Cost Savings Associated with an Extended-Release Opioid with Abuse-Deterrent Technology in the U.S. Journal of Medical Economics. 2014; 17(4): 279-287.

36. **Michna E**, Wasan A, Edwards R, Katz J, Nedeljkovic S et al. Psychiatric Comorbidity Is Associated Prospectively with Diminished Opioid Analgesia and Increased Opioid Misuse in Patients with Chronic Low Back Pain. Anesthesiology. 2015; 123: 861-872.

37. Pollak K, Stephens L, Posner K, Rathmell J, Fitzgibbon D, Dutton R, **Michna E**, Domino K. Trends in Pain Medicine Liability. Anesthesiology. 2015; 123: 1133-1141.

38. Bartoli A, **Michna E**, He E, Wen W. Efficacy and safety of once-daily, extended-release hydrocodone in individuals previously receiving hydrocodone/acetaminophen combination therapy for chronic pain. Postgraduate Medicine. 2015; 127(1): 5-12.

39. Bartoli A, **Michna E**, He E, Wen W. Pain intensity and interference with functioning and well-being in subgroups of patients with chronic pain treated with once-daily hydrocodone tablets. Journal of Opioid Management. 2015; 11(6): 519-533.

40. Abrecht C, Gabriel R, Dutton R, Kaye A, **Michna E**, Urman R. National Perioperative Outcomes for Intrathecal Pump, Spinal Cord Stimulator, and Peripheral Nerve Stimulator Procedures. Pain Physician. 2015; 18: 547-554.

41. Fitzgibbon D, Stephens L, Posner K, **Michna E**, Rathmell J et al. Injury and Liability Associated with Implantable Devices for Chronic Pain. Anesthesiology. 2016; 124: 1384-1393.

42. Edwards R.R., Dolman A.J, **Michna E** et al. Changes in Pain Sensitivity and Pain Modulation During Oral Opioid Treatment: The Impact of Negative Affect. Pain Medicine. 2016; 17(10): 1882-1891.

43. Pollak K, Stephens L, Posner K, Rathmell J, Fitzgibbon D, Dutton R, **Michna E**, Domino K. Trends in Pain Medicine Liability. Survey of Anesthesiology. 2016; 60(3): 130-131.

44. Webster L, **Michna E**, Khan A, Israel R, Harper J. Long-Term Safety and Efficacy of Subcutaneous Methylnaltrexone in Patients with Opioid-Induced Constipation and Chronic Noncancer Pain: A Phase 3, Open-Label Trial. Pain Med. 2017; 18(8): 1496-1504.

Non-peer Reviewed Scientific or Medical Publications/Materials in print or other media

Proceedings of Meetings:

1. Mason KP, **Michna E**, Zurakowski D, Koka B, Hickok SE, Burrows PE. Serum alcohol levels after ethanol embolization and sclerotherapy in children. In: ;1999.

2. Mason KP, **Michna E**, Burrows PE, Koka BV. Anesthetic management of hepatic hemangiomas. In: February 19-21, 1999; Las Vegas, Nevada. 1999.

3. Mason KP, **Michna E**, Zurakowski D, Burrows PE. Serum alcohol levels after ethanol embolotherapy or sclerotherapy of vascular anomalies in children and adults. In: 13th. May, 2000; Montreal, Canada. ;2000.

4. Jamison R, **Michna E**, Hynes W, Nedeljkovic S, Soumekh S, Janfaza D, Ross E. Predicting Problems with Opioids in High-Risk Chronic Pain. In: August 2002; San Diego, CA;2002. p.

5. Rossiter L, Kirson NY, Shei A, White AG, Birnbaum HG, Ben-Joseph R, **Michna E.** Estimating the Societal Economic Impact of Abuse-deterrent Formulations of Long-acting Opioids in the U.S. Research support was provided to Analysis Group, Inc. by Purdue Pharma L.P. 2013 AcademyHealth Annual Research Meeting (ARM)

Reviews, Chapters, Monographs and Editorials:

1. **Michna E**. Legal Aspects of Pain Management (Part 1). New England Pain Association Newsletter. 1999;4(2).

2. **Michna E**. Legal Aspects of Pain Management (Part 2). New England Pain Association Newsletter. 1999;4(3).

3. **Michna E**. Acute Postoperative Pain Management. In Bailin M, editor. Harvard Electronic Anesthesia Library (CD ROM). Philadelphia: Lippincott Williams & Wilkins. 2001.

4. **Michna E**, Mason KP. AIDS and the healthcare worker. In: S.S. Nedeljkovic (ed.), Pain management, anesthesia, and HIV/AIDS. Boston, MA: Butterworth Heinemann;2002. p. 187-193.

5. **Michna E**, Mason KP. Legal aspects of pain management. In: Warfield C, H Fauset, editors. Manual of Pain Management. Philadelphia, PA: Lippincott Williams & Wilkins;2002. p. 385-389.

6. Ross E, **Michna E.** Pain, Invasive Procedures for. In: Aminoff M, Daroff, R, editors. Encyclopedia of Neurological Sciences. San Diego, CA: Academic Press;2003. p. 740-750.

7. **Michna E**, Pananero S. Anesthetic Management in Patients with Musculoskeletal Disease. In Pian- Smith MCM and Leffert I. Editors: Obsetric Anesthesia. New York: PocketMedicine.com, Inc;2005

Abstract

1. Duh, MS; Vekeman F, Korves C, Lefebvre P, Dial E, Latrmoeuille-Viau D, Wei R, Stangle B, Lafeuille M, **Michna E**, Greenberg P. International Society for Pharmacoepidemiology (ISPE). 2010

2. **Michna E.** Subcutaneous Methylnaltrexone for the Treatment of Opioid-Induced Constipation in Patients with Chronic Non-Malignant Pain. Australian Pain Society & New Zealand Pain Society Combined Annual Scientific Meeting. 2010

3. **Michna E**, Cheng W, Korves C, Schaaf D, Andrews R, Zhou Z, Mardekian J, Joshi AV, Birnbaum H, Duh MS. A meta-analysis of efficacy and safety of prescription opioids, including formulations with tamper-resistant technologies, in non-cancer pain management. Value in Health 2013; 16(3):A111.

4. **Michna E**, Kirson NY, Shei A, White A, Birnbaum HG, Ben-Joseph R, Rossiter LF. Estimating the payer-specific excess medical costs of opioid abuse in the United States. Value in Health 2013; 16(3):A124.

Experience as Testifying Expert

Depomed, Inc., v. Purdue Pharma L.P., The P.F. Laboratories, INC., And Purdue Pharmaceutical L.P., **U.S. District Court NJ,** Civil Action No. 3:13-00571 (BRM/TJB)

Purdue Pharma L.P., v. Watson Laboratories, Inc., **U.S. District Court DE**, C.A. No. 14-1227 (SLR)(SRF)

Purdue Pharma L.P., v. Watson Laboratories, Inc., **U.S. District Court DE**, C.A. No. 14-1410 (SLR)(SRF)

Purdue Pharma L.P., v. Actavis Laboratories UT, Inc., **U.S. District Court DE**, C.A. No. 15-192 (SLR)(SRF)

In the Matter of Impax Laboratories, Inc. U.S. FTC Offfice of Administrative Law Judges, Docket No. 9373

State of Oklahoma v. Purdue Pharma, L.P., et al., **U.S. District Court OK,** C.A. No. CJ-2017-816

Narrative Report:

My role as a teacher and mentor takes place predominantly at the Pain Management Center at the Brigham and Women's Hospital, where I work with and teach anesthesia residents and pain fellows, internal medicine residents, and palliative care fellows on a daily basis. My clinical teaching responsibilities encompass the mentoring, teaching, and supervising of medical students, residents, and our pain fellows in the Pain Management Center. Every Monday I participate in the morning rounds at the Pain Management Center where one of our fellows, residents, or attending physicians present a lecture topic. I enjoy teaching, and I believe the residents and fellows benefit from my perspective and experience in particular how to manage the very complicated chronic pain patients. I was awarded the teacher of the year award by our fellows in 2007 and consistently rated very highly for teaching by the pain management fellows.

I also am a yearly invited lecturer on the topic of "Legal Aspects of Pain Medicine" at the Tufts University Medical School's Masters Program in Pain Medicine, and also the Harvard Medical School's HST course on the topic of "Opioids for Chronic Pain".

As a former medical malpractice trial attorney, I have knowledge and experience in the field of medical malpractice. I write and lecture both on the legal aspects of pain management and on medical malpractice.

I have been an invited speaker at the local, regional, and national level on various topics concerning pain management including the legal aspects of prescribing opioid medications. I recently directed a workshop at the annual ASA meeting on “Depositions and Testimonies”. I have been an invited speaker at other medical specialties annual meetings including the International Pelvic Pain Society and the Society of Interventional Radiology.

As Director of the Pain Trial Center, I provided leadership to a center that had previously had minimal funding, few sponsors and a paucity of active trials. I am proud to be currently overseeing a Pain Trial Center that provides excellent service to the clinical sponsors and our patients.

Appendix B

Materials Considered

Court Documents

Buckman Co. v. Plaintiffs' Legal Comm., 531 U.S. 341, 351 n.5 (2001)

Deposition of Andrew Boyer, In Re: National Prescription Opiate Litigation MDL No. 2804, United States District Court for the Northern District of Ohio, Eastern Division, January 15, 2019.

Deposition of David S. Egilman M.D., MPH, *In Re: National Prescription Opiate Litigation*, MDL No. 2804, United States District Court, Northern District of Ohio, Eastern Division, April 25, 2019.

Deposition of Mark A. Schumacher, M.D., Ph.D., *In Re: National Prescription Opiate Litigation*, MDL No. 2804, United States District Court for the Northern District of Ohio, Eastern Division, April 23, 2019.

Deposition of Matthew Perri III, *In Re: National Prescription Opiate Litigation*, MDL No. 2804, United States District Court for the Northern District of Ohio, Eastern Division, April 24, 2019.

Deposition of Meredith Rosenthal, *In Re: National Prescription Opiate Litigation*, MDL No. 2804, United States District Court for the Northern District of Ohio, Eastern Division, May 4, 2019.

Expert Report of Anna Lembke, M.D., *In Re: National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019.

Expert Report of David Kessler, M.D., *In Re: National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019.

Expert Report of David S. Egilman, M.D., MPH, *In Re: National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019.

Expert Report of Katherine Keyes, Ph.D, MPH, *In Re: National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019.

Expert Report of Mark A. Schumacher, M.D., Ph.D., *In Re: National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019.

Expert Report of Matthew Perri III, *In Re: National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019.

Expert Report of Professor Meredith Rosenthal, *In Re: National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019.

Expert Report of Scott L. Wexelblatt, M.D., *In Re: National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019.

Expert Report of Ted Miller, Ph.D., *In Re: National Prescription Opiate Litigation*, MDL No. 2804, March 25, 2019.

Summit County, Cuyahoga County, and the Cities of Akron and Cleveland, Ohio Plaintiffs' Responses and Objections to Manufacturer Defendants' Fourth Set of Interrogatories, *In Re: National Prescription Opiate Litigation*, Case No. 17-md-2804, United States District Court for the Northern District of Ohio Eastern Division.

Third Amended Corrected Complaint, *In Re: National Prescription Opiate Litigation*, MDL No. 2804, May 29, 2018.

Washington Legal Found. v. Friedman, 13 F. Supp. 2d 51, 56 (D.D.C. 1998)

Bates-Stamped Documents

"Actiq Marketing Materials," TEVA_MDL_A_00695218-6810.

"Actiq TIRF REMS Documentation," TEVA_MDL_A_00709777-10056.

"Fentora Marketing Materials," TEVA_MDL_A_00025238-33471.

"Fentora TIRF REMS Documentation," TEVA_MDL_A_00710057-205.

"Policy on Third-Party Funding Requests to Support Independent Medical Education Programs," TEVA_MDL_A_06880639-55.

Anesta Corporation, and Abbott Laboratories, "Actiq Risk Management Program," November 4, 1998, TEVA_MDL_A_00564336-65.

Cephalon, Inc., "Fentora RiskMAP," September 18, 2006, TEVA_MDL_A_00265075-425.

Cephalon, Inc., "Important Safety Information for Fentora," September 10, 2007, TEVA_MDL_A_00970847-50.

Publicly Available Documents

21 C.F.R. § 202.1

21 C.F.R. § 312.2

"Actiq Label, November 1998," 1998. https://www.accessdata.fda.gov/drugsatfda_docs/label/1998/20747lbl.pdf.

"Fentora Label, September 2006," 2006. https://www.accessdata.fda.gov/drugsatfda_docs/label/2006/021947lbl.pdf.

"Statement from FDA Commissioner Scott Gottlieb, M.D. on the agency's 2019 policy and regulatory agenda for continued action to forcefully address the tragic epidemic of opioid abuse." February 29, 2019. Available at https://www.fda.gov/news-events/press-announcements/statement-fda-commissioner-scott-gottlieb-md-agencys-2019-policy-and-regulatory-agenda-continued, accessed April 4, 2019.

Abernathy, Amy P., Jane L. Wheeler, and Barry V. Fortner. "A Health Economic Model of Breakthrough Pain." *American Journal of Managed Care* Vol. 14, No. 5 (2008): pp. S129-S40.

Akinboro, Oladimeji Akinola et al., "Opioid Use Is NOT Associated with in-Hospital Mortality Among Patients with Sickle CELL Disease in the United States: Findings from the National Inpatient Sample." *Blood* Vol. 132, Supplement 1: 315 (2018).

American Pain Foundation, "Treatment Options: A Guide for People Living with Pain."

Ashburn, Michael A., Kieran A. Slevin, John Messina, and Fang Xie. "The efficacy and safety of fentanyl buccal tablet compared with immediate-release oxycodone for the management of breakthrough pain in opioid-tolerant patients with chronic pain." *Anesthesia & Analgesia* Vol. 112, No. 3 (2011): pp. 693-702.

Bennett, Daniel S., "Breakthrough Pain: Treatment Rationale With Opioids," https://www.medscape.org/viewarticle/461612, accessed April 11, 2018.

Brennan, Michael J., Steven D. Passik, and Kenneth L. Kirsh, "Pharmacologic Management of Breakthrough or Incident Pain," 2003. https://www.medscape.org/viewarticle/449803, accessed April 11, 2019.

Burton, Beth and Giovambattista Zeppetella. "Assessing the impact of breakthrough cancer pain." *British Journal of Nursing* Vol. 20, Supplement 5 (2011): pp. S14-S19.

Caraceni, Augusto, Andrew Davies, Philippe Poulain, Hernán Cortés-Funes, Sunil J. Panchal, and Guido Fanelli. "Guidelines for the management of breakthrough pain in patients with cancer." *Journal of the National Comprehensive Cancer Network* Vol. 11, Supplement 1 (2013): pp. S-29-S-36.

Cephalon, Inc., Form 10-K405, filed March 30, 2001.

Cephalon, Inc., *Opioid Medications and REMS: A Patient's Guide*, 2010.

Cephalon, Inc., *Special Report: An Integrated Risk Evaluation and Mitigation Strategy for Fentanyl Buccal Tablet (Fentora) and Oral Transmucosal Fentanyl Citrate (Actiq)*, 2011.

Chang, Andrew, Eric J. Roeland, Rabia S. Atayee, Carolyn Revta, and Joseph D. Ma. "Transmucosal immediate-release fentanyl for breakthrough cancer pain: opportunities and challenges for use in palliative care." *Journal of Pain & Palliative Care Pharmacotherapy* Vol. 29, No. 3 (2015): pp. 247-60.

Chou, Roger, et al., "Clinical guidelines for the use of chronic opioid therapy in chronic noncancer pain." *The Journal of Pain* Vol. 10, No. 2 (2009): pp. 113-30. e22.

CMS, *Pharmacy Self-Auditing*, December 2015.

Collett, B. J. "Chronic opioid therapy for non-cancer pain." *British Journal of Anaesthesia* Vol. 87, No. 1 (2001): pp. 133-43.

Coluzzi, Paul H. et al., "Breakthrough cancer pain: a randomized trial comparing oral transmucosal fentanyl citrate (OTFC®) and morphine sulfate immediate release (MSIR®)." *Pain* Vol. 91 (2001): pp. 123-30.

Dahlhamer J, et al., "Prevalence of Chronic Pain and High-Impact Chronic Pain Among Adults — United States," 2016. Morbidity and Mortality Weekly Report (2018), 67:1001–1006, https://www.cdc.gov/mmwr/volumes/67/wr/mm6736a2.htm, accessed May 9, 2019.

FDA, *Addendum to the FDA briefing information to summarize TIRF REMS issues relevant to the August 3, 2018 meeting*, July 25, 2018.

FDA, "Approved Risk Evaluation and Mitigation Strategies," September 7, 2017, https://www.accessdata.fda.gov/scripts/cder/rems/index.cfm?event=RemsDetails.page&REMS=60, accessed February 14, 2019.

FDA, "Development & Approval Process (Drugs)," https://www.fda.gov/Drugs/DevelopmentApprovalProcess/default.htm, accessed February 14, 2019.

FDA, "FDA's Role in Managing Medication Risks," https://www.fda.gov/Drugs/DrugSafety/REMS/ucm592672.htm, accessed February 13, 2019.

FDA, "FDA Approved Drug Products, Fentora," https://www.accessdata.fda.gov/scripts/cder/daf/index.cfm?event=overview.process&ApplNo=021947, accessed February 19, 2019.

FDA, "Good Reprint Practices for the Distribution of Medical Journal Articles and Medical or Scientific Reference Publications on Unapproved New Uses of Approved Drugs and Approved or Cleared Medical Devices," January 13, 2009, https://www.fda.gov/regulatory-information/search-fda-guidance-documents/good-reprint-practices-distribution-medical-journal-articles-and-medical-or-scientific-reference, accessed February 14, 2019.

FDA, *Guidance for Industry, Development and Use of Risk Minimization Action Plans*, March 2005. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm071616.pdf.

FDA, "A Guide to Safe Use of Pain Medicine," https://www.fda.gov/ForConsumers/ConsumerUpdates/ucm095673.htm, accessed April 4, 2019.

FDA, *An Introduction to the Improved FDA Prescription Drug Labeling*, 2006.

FDA, *Managing the Risks From Medical Product Use Creating a Risk Management Framework*, May 1999. https://hdl.handle.net/2027/umn.31951d016951490.

FDA, *Medical Product Communications That Are Consistent With the FDA-Required Labeling — Questions and Answers; Guidance for Industry*, June 2018. https://www.fda.gov/downloads/drugs/guidancecomplianceregulatoryinformation/guidances/ucm537130.pdf.

FDA, "'Off-Label' and Investigational Use Of Marketed Drugs, Biologics, and Medical Devices - Information Sheet," July 12, 2018, http://www.fda.gov/RegulatoryInformation/Guidances/ucm126486.htm, accessed April 23, 2019.

FDA, "Standardizing and Evaluating Risk Evaluation and Mitigation Strategies," 2014.

FDA. "Use of Approved Drugs for Unlabeled Indications." *FDA Drug Bulletin* Vol. 12, No. 1 (April, 1982).

FDA CDER, *MAPP 6700.1: Risk Management Activities in OND and ODS, Manual of Policies and Procedures*.

Fine, Perry G., John Messina, Fang Xie, and James Rathmell. "Long-term safety and tolerability of fentanyl buccal tablet for the treatment of breakthrough pain in opioid-tolerant patients with chronic pain: an 18-month study." *Journal of Pain and Symptom Management* Vol. 40, No. 5 (2010): pp. 747-60.

Fine, Perry G., Christine Miaskowski, and Michael Brennan, *SELECT (Stratify, Examine, Listen, Evaluate, Control, Tailor): Opioid-Based Management of Persistent and Breakhrough Pain*, 2008.

Fishbain, David A., Brandly Cole, John Lewis, Hubert L. Rosomoff, and R. Steele Rosomoff. "What percentage of chronic nonmalignant pain patients exposed to chronic opioid analgesic therapy develop abuse/addiction and/or aberrant drug-related behaviors? A structured evidence-based review." *Pain Medicine* Vol. 9, No. 4 (2007): pp. 444-59.

Fishman, Scott M. *Responsible Opioid Prescribing: A Physician's Guide.* Washington, DC: Waterford Life Sciences, 2007.

Fortner, Barry V., Theodore A. Okon, and Russell K. Portenoy. "A survey of pain-related hospitalizations, emergency department visits, and physician office visits reported by cancer patients with and without history of breakthrough pain." *The Journal of Pain* Vol. 3, No. 1 (2002): pp. 38-44.

Furlan, Andrea D., Juan A. Sandoval, Angela Mailis-Gagnon, and Eldon Tunks. "Opioids for chronic noncancer pain: a meta-analysis of effectiveness and side effects." *CMAJ* Vol. 174, No. 11 (2006): pp. 1589-94.

Gottlieb, Scott., *Remarks by Dr. Gottlieb at the FDA Online Opioid Summit*, June 27, 2018. https://www.fda.gov/NewsEvents/Speeches/ucm611945.htm.

Haythornthwaite, Jennifer A., Lynette A. Menefee, Amy L. Quatrano-Piacentini, and Marco Pappagallo. "Outcome of Chronic Opioid Therapy for Non-Cancer Pain." *Journal of Pain and Symptom Management* Vol. 15, No. 3 (1998): pp. 185-94.

Jamison, Robert N., Edgar L. Ross, Edward Michna, Li Q. Chen, Caroline Holcomb, and Ajay D. Wasan. "Substance Misuse Treatment for High Risk Chronic Pain Patients on Opioid Therapy: A Randomized Trial." *Pain* Vol. 150, No. 3 (2010): pp. 390-400.

Jamison, Robert N., Juliana Serraillier, and Edward Michna. "Assessment and Treatment of Abuse Risk in Opioid Prescribing for Chronic Pain." *Pain Research and Treatment* Vol. 2011 (2011): pp. 1-12.

Kalso, Eija, Jayne E. Edwards, R. Andrew Moore, and Henry J. McQuay. "Opioids in chronic non-cancer pain: systematic review of efficacy and safety." *Pain* Vol. 112, No. 3 (2004): pp. 372-80.

Kesselheim, Aaron S. et al., "A Randomized Study of How Physicians Interpret Research Funding Disclosures." *New England Journal of Medicine* Vol. 367, No. 12 (2012): pp. 1119-27.

Lacasse, Jeffrey R., and Jonathan Leo. "Knowledge of ghostwriting and financial conflicts-of-interest reduces the perceived credibility of biomedical research." *BMC Research Notes* Vol. 4, No. 27 (2011): pp. 1-6.

Levy, Benjamin, Leonard Paulozzi, Karin A. Mack, and Christopher M. Jones. "Trends in Opioid Analgesic–Prescribing Rates by Specialty, U.S., 2007–2012." *American Journal of Preventive Medicine* Vol. 49, No. 3 (2015): pp. 409-13.

Mercadante, Sebastiano, Claudio Adile, Francesco Masedu, Paolo Marchetti, Andrea Costanzi, and Federica Aielli. "Factors influencing the use of opioids for breakthrough cancer pain: A secondary analysis of the IOPS-MS study." *European Journal of Pain* Vol. 23, No. 4 (2018): pp. 719-26.

Mercadante, Sebastiano et al., Steering Committee of the European Association for Palliative Care Research Network. "Episodic (breakthrough) pain: consensus conference of an expert working group of the European Association for Palliative Care." *Cancer* Vol. 94, No. 3 (2002): pp. 832-39.

Michna, Edward et al., "Predicting Aberrant Drug Behavior in Patients Treated for Chronic Pain: Importance of Abuse History." *Journal of Pain and Symptom Management* Vol. 28, No. 3 (2004): pp. 250-58.

Minkowitz, Harold, Janet Bull, R. Charles Brownlow, Neha Parikh, and Richard Rauck. "Long-term safety of fentanyl sublingual spray in opioid-tolerant patients with breakthrough cancer pain." *Supportive Care in Cancer* Vol. 24, No. 6 (2016): pp. 2669-75.

Nalamachu, Srinivas, et al., *Prescription Pain Medication: Preserving Patient Access While Curbing Abuse*, 2013.

Nalamachu, Srinivas, David Hassman, Mark S Wallace, Sam Dumble, Rob Derrick, and Julian Howell. "Long-term effectiveness and tolerability of sublingual fentanyl orally disintegrating tablet for the treatment of breakthrough cancer pain." *Current Medical Research and Opinion* Vol. 27, No. 3 (2011): pp. 519-30.

National Archives And Records Administration. (1972) Federal Register: 37 Fed. Reg. 16,503-16,504.

National Archives And Records Administration. (1975) Federal Register: 40 Fed. Reg. 15,392, 15,394.

National Archives And Records Administration. (1994) Federal Register: 59 Fed. Reg. 59,820, 59,821, 59,825.

National Archives And Records Administration. (1998) Federal Register: 63 Fed. Reg. 31,143, 31,153, 64,556, 64,579.

National Archives And Records Administration. (2003) Federal Register: 68 Fed. Reg. 6,062, 6,071.

Noble, Meredith et al., "Long-term opioid management for chronic noncancer pain." *The Cochrane Database of Systematic Reviews* Vol. 1 (2010): pp. 1-69.

Passik, S. D., and K. L. Kirsh. "Weighing in on the off-label use of Actiq for noncancer-related pain: a recipe for success or a recipe for disaster?" *Pain Medicine* Vol. 8, No. 2 (2007): pp. 130-3.

Passik, Steven D., John Messina, Anthony Golsorkhi, and Fang Xie. "Aberrant Drug-Related Behavior Observed During Clinical Studies Involving Patients Taking Chronic Opioid Therapy for Persistent Pain and Fentanyl Buccal Tablet for Breakthrough Pain." *Journal of Pain and Symptom Management* Vol. 41, No. 1 (2011): pp. 116-25.

Payne, Richard. "Recognition and diagnosis of breakthrough pain." *Pain Medicine* Vol. 8, Supplement 1 (2007): pp. S3-S7.

Portenoy, Russell K., Daniel S. Bennett, Richard Rauck, Steven Simon, Donald Taylor, Michael Brennan, and Steven Shoemaker. "Prevalence and characteristics of breakthrough pain in opioid-treated patients with chronic noncancer pain." *The Journal of Pain* Vol. 7, No. 8 (2006): pp. 583-91.

Portenoy, Russell K., Daniel Bruns, Bonnie Shoemaker, and Steven A. Shoemaker. "Breakthrough pain in community-dwelling patients with cancer pain and noncancer pain, part 1: prevalence and characteristics." *Journal of Opioid Management* Vol. 6, No. 2 (2010): pp. 97-108.

Rudowska, Joanna. "Management of breakthrough pain due to cancer." *Contemporary Oncology* Vol. 16, No. 6 (2012): pp. 498-501.

Schuckit, Marc A. "Treatment of opioid-use disorders." *New England Journal of Medicine* Vol. 375, No. 4 (2016): pp. 357-68.

Shimoyama, Naohito, et al., "Efficacy and safety of sublingual fentanyl orally disintegrating tablet at doses determined from oral morphine rescue doses in the treatment of breakthrough cancer pain." *Japanese Journal of Clinical Oncology* Vol. 45, No. 2 (2015): pp. 189-96.

Simpson, Richard K., Everton A. Edmondson, Charles F. Constant, and Connie Collier. "Transdermal fentanyl as treatment for chronic low back pain." *Journal of Pain and Symptom Management* Vol. 14, No. 4 (1997): pp. 218-24.

Slatkin, Neal E. and Rhiner, Michele I., "Breakthrough Pain: Improving Recognition and Management to Enhance Quality of Life," 2008. www.medscape.org/viewarticle/572129, accessed October 10, 2017.

Smith, Howard. "A comprehensive review of rapid-onset opioids for breakthrough pain." *CNS Drugs* Vol. 26, No. 6 (2012): pp. 509-35.

Substance Abuse and Mental Health Services Administration (SAMHSA), "The CBHSQ Report: How People Obtain the Prescription Pain Relievers they Misuse," 2017. https://www.samhsa.gov/data/sites/default/files/report_2686/ShortReport-2686.html, accessed March 6, 2019.

Taylor, Donald R., Lynn R. Webster, Steven Y. Chun, Jeffrey Reinking, Mary Stegman, Steven Shoemaker, and Barry V. Fortner. "Impact of Breakthrough Pain on Quality of Life in Patients with Chronic, Noncancer Pain: Patient Perceptions and Effect of Treatment with Oral Transmucosal Fentanyl Citrate (OTFC, ACTIQ)." *Pain Medicine* Vol. 8, No. 3 (2007): pp. 281-88.

TIRF REMS Access, "Education Program for Prescribers and Pharmacists," https://www.tirfremsaccess.com/TirfUI/rems/pdf/education-and-ka.pdf.

TIRF REMS Access, "Frequently Asked Questions," https://www.tirfremsaccess.com/TirfUI/rems/pdf/faq.pdf.

TIRF REMS Access, "Knowledge Assessment," https://www.tirfremsaccess.com/TirfUI/rems/pdf/education-and-ka.pdf.

TIRF REMS Access, "Patient-Prescriber Agreement Form," https://www.tirfremsaccess.com/TirfUI/rems/pdf/ppaf-form.pdf.

TIRF REMS Access, "Prescriber Enrollment Form," https://www.tirfremsaccess.com/TirfUI/rems/pdf/prescriber-enrollment-form.pdf.

U.S. Drug Enforcement Administration, "Practitioner's Manual - Section V - Valid Prescription Requirements," https://www.deadiversion.usdoj.gov/pubs/manuals/pract/section5.htm, accessed April 24, 2019.

U.S. Drug Enforcement Agency, "Drug Scheduling," https://www.dea.gov/drug-scheduling, accessed April 24, 2019.

Vowles, Kevin E., Mindy L. McEntee, Peter Siyahhan Julnes, Tessa Frohe, John P. Ney, and David N. van der Goes. "Rates of opioid misuse, abuse, and addiction in chronic pain: a systematic review and data synthesis." *Pain* Vol. 156, No. 4 (2015): pp. 569-76.

Webster, Lynn R., Kieran A. Slevin, Arvind Narayana, Craig Q. Earl, and Ronghua Yang. "Fentanyl buccal tablet compared with immediate-release oxycodone for the management of breakthrough pain in opioid-tolerant patients with chronic cancer and noncancer pain: a randomized, double-blind, crossover study followed by a 12-week open-label phase to evaluate patient outcomes." *Pain Medicine* Vol. 14, No. 9 (2013): pp. 1332-45.

Webster, Lynn R. and M. Beth Dove, "Optimizing Opioid Treatment for Breakthrough Pain," 2007. www.medscape.org/viewarticle/563417, accessed October 10, 2017.